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(56) Documents cited
 GB 1525958
 GB 1500043
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(58) Field of search
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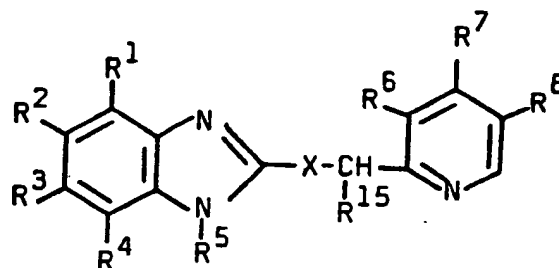
(71) Applicants
 Aktiebolaget Hassle,
 (Sweden),
 S-431 83 Molndal,
 Sweden

(72) Inventors
 Arne Elof Brandstrom
 Stig Ake Ingemar
 Carlsson
 Britt Inger Monica
 Kallsson
 Per Lennart Lindberg

(74) Agent and/or
 Address for Service
 J. A. Kemp & Co.,
 14 South Square,
 Gray's Inn,
 London WC1R 5EU

(54) Novel pharmacologically active
 compounds

(57) Novel compounds of the formula:



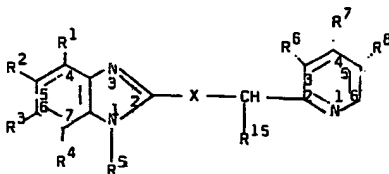
wherein X is S or SO and R¹, R², R³, R⁴,
 R⁵, R⁶, R⁷, R⁸ and R¹⁵ are organic
 residues, pharmaceutical compositions
containing such compounds particularly
for use in the treatment of gastric
disorders.

SPECIFICATION

Novel pharmacologically active compounds

- 5 The object of the present invention is to provide novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and provide gastrointestinal cytoprotective effects and thus can be used in the prevention and treatment of peptic ulcer.

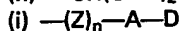
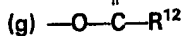
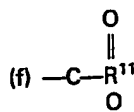
- The present invention relates to the use of the compounds of the invention or therapeutically acceptable salts thereof, for inhibiting gastric acid secretion as well as providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, the compounds may be used for prevention and treatment of other gastrointestinal disorders, where cytoprotective and/or gastric anti-secretory effect is desirable e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive ethanol consumption. The invention also relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds and to novel intermediates in the preparation of the compounds of the invention.
- 35 Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the British patent specifications 1 500 043 and 1 525 958, in the US patent 4 182 766, in the European patent specification 0 005 129, and in the Belgian patent specification 890 024. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory disease are disclosed in the European patent application with publication no. 0 045 200.
- 45 It has been found that the compounds of the formula



wherein

X is —S— or —S— ;
 R^{15} is H, CH_3 or C_2H_5 ;

- 50 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 , which are the same or different, are
 (a) H
 (b) halogen
 (c) —CN
 (d) —CHO
 55 (e) —CF_3



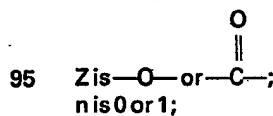
- 60 (j) aryl
 (k) aryloxy
 (l) alkylthio containing 1-6 carbon atoms
 (m) —NO_2
 (n) alkylsulfinyl containing 1-6 carbon atoms

- 65 or wherein
 (o) adjacent groups $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from N and O, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

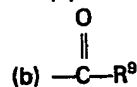


whereby if $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12} , which are the same or different, are

- (a) aryl,
 (b) alkoxy containing 1-4 carbon atoms,
 (c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part,
 85 (d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part,
 (e) aryloxy,
 (f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
 90 (g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms
 R^{13} is (a) alkyl containing 1-4 carbon atoms, or
 (b) alkylene containing 2-3 carbon atoms;



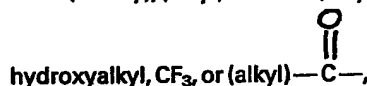
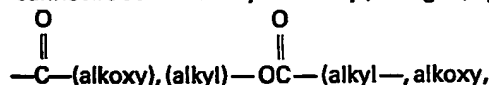
- A is (a) alkylene containing 1-6 carbon atoms
 (b) cycloalkylene containing 3-6 carbon atoms
 (c) alkenylene containing 2-6 carbon atoms
 100 (d) cycloalkenylene containing 3-6 carbon atoms,
 or
 (e) alkynylene containing 2-6 carbon atoms;
 D is (a) —CN




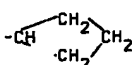
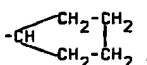
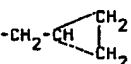
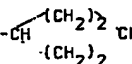
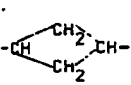
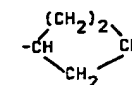
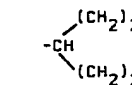
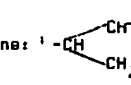
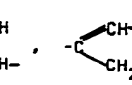
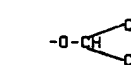
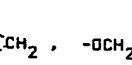
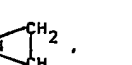

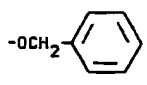
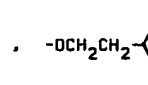
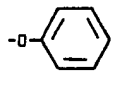
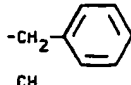
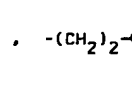
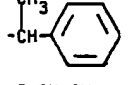
- 105 (c) $\text{—(Y)}_m\text{—(C)}_r\text{—R}^{10}$
 wherein
 R^9 is (a) alkoxy containing 1-5 carbon atoms, or

- (b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;
 m is 0 or 1;
 r is 0 or 1;
- 5 Y is (a) —O—
 (b) —NH—
 (c) —NR¹⁰—;
 R¹⁰ is (a) H
- 10 (b) alkyl containing 1-3 carbon atoms,
 (c) arylalkyl containing 1-2 carbon atoms in the alkyl part, or
 (d) aryl;
 R⁵ is (a) H or
- $$\begin{array}{c} \text{O} \\ || \\ \text{—C—R}^{14}; \end{array}$$
- 15 wherein
 R¹⁴ is (a) alkyl containing 1-6 carbon atoms,
 (b) arylalkyl containing 1-2 carbon atoms in the alkyl part
 (c) aryl
- 20 (d) alkoxy containing 1-4 carbon atoms
 (e) arylalkoxy containing 1-2 carbon atoms in the alkyl part
 (f) aryloxy
 (g) amino
- 25 (h) mono- or dialkylamino containing 1-4 carbon atoms in the alkyl part(s)
 (i) arylalkylamino containing 1-2 carbon atoms in the alkyl part
 (j) arylamino;
- 30 R⁶ and R⁸, which are the same or different, are
 (a) H or
 (b) alkyl containing 1-5 carbon atoms;
 R⁷ is (a) H
- 35 (b) alkyl containing 1-8 carbon atoms
 (c) alkoxy containing 1-8 carbon atoms
 (d) alkenyloxy containing 2-5 carbon atoms
 (e) alkynyloxy containing 2-5 carbon atoms
 (f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
- 40 (g) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
 (h) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
- 45 (i) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
 (j) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
 (k) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
- 50 (l) R⁶ and R⁷, or R⁷ and R⁸ together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R⁶ and R⁷, or R⁷ and R⁸, is
- 55 —CH=CH—CH=CH—
 —O—(CH₂)_p—
 —CH₂(CH₂)_p—
 —O—CH=CH—
 —NH—CH=CH—
 —N—CH=CH—
- 60 |
 CH₃
- wherein p is 2, 3 or 4 and the O and N atoms always

- are attached to position 4 in the pyridine ring;
 and physiologically acceptable salts of the compounds I where in X is S;
- 65 with the proviso that
 (a) not more than one of R⁶, R⁷ and R⁸ is hydrogen,
 (b) when X is SO, R⁵ is H and R⁶, R⁷ and R⁸ are selected only from hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R¹, R², R³ and R⁴ are hydrogen, then R¹, R², R³ and R⁴ cannot be selected only from alkyl groups, halogen, alkoxy, alkoxyalkyl, alkoxy or alkanoyl,
- 70 (c) when X is S, R⁵ is H, alkanoyl or alkoxyalkyl, and R⁶, R⁷ and R⁸ are selected only from hydrogen, methyl, ethyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R¹, R², R³ and R⁴ are hydrogen, then R¹, R², R³ and R⁴ cannot be selected only from alkyl groups, halogen, alkoxy, alkanoyl, trifluoromethyl, or NO₂,
- 80 (d) when X is SO, one of R⁶, R⁷ and R⁸ is H and the other two of R⁶, R⁷ and R⁸ are alkyl, and at the same time more than one of R¹, R², R³ and R⁴ are hydrogen, then those radicals R¹, R², R³ and R⁴ which are not H cannot be selected only from alkyl, halogen, cyano,

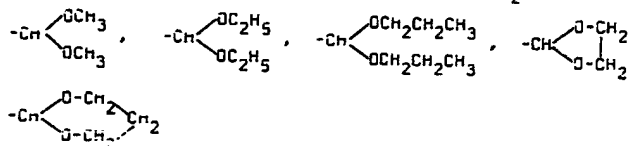


- 90 (e) when R³, R⁴, R⁵ and R¹⁵ are H and simultaneously R⁶ and R⁸ are H or CH₃ and R⁷ is OCH₃, then R¹ is not CF₃ when R² is H, and R² is not CF₃ when R¹ is H, are effective as gastrointestinal cytoprotectives and as inhibitors of gastric acid secretion in mammals and man as stated above.
- 95 Illustrative examples of the various radicals in the formula I are as follows. These illustrative examples will be applicable to different radicals depending on the number of carbon atoms prescribed for each radical. It will be understood that the expressions "alkyl" and "alkoxy" include straight, branched and cyclic structures.

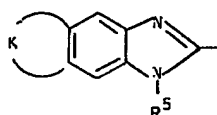
Halogen:	F, Cl, Br, I
Alkyl:	CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$, $n\text{-C}_4\text{H}_9$, $\text{sec.-C}_4\text{H}_9$, $\text{iso.-C}_4\text{H}_9$, $\text{tert.-C}_4\text{H}_9$, $n\text{-C}_5\text{H}_{11}$, $n\text{-C}_6\text{H}_{13}$,  ,  ,  ,  , 
Alkylene:	$-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_3-$, $-\text{CH}_2-\text{CH}-$, $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$, $-(\text{CH}_2)_6-$
Cycloalkylene:	 ,  , 
Alkenylene:	$-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$, $-(\text{CH}_2)_2-\text{CH}=\text{CH}-\text{CH}_2-$, $-(\text{CH}_2)_3-\text{CH}=\text{CH}-\text{CH}_2-$
Alkylthio:	$-\text{S}-\text{CH}_3$, $-\text{S}-\text{C}_2\text{H}_5$, $-\text{S}-i\text{-C}_3\text{H}_7$
Cycloalkenylene:	 , 
Alkynylene:	$-\text{C}\equiv\text{C}-$, $-\text{CH}_2-\text{C}\equiv\text{C}-$
Alkoxy:	$-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{O}-n\text{-C}_3\text{H}_7$, $-\text{O}-i\text{-C}_3\text{H}_7$, $-\text{O}-n\text{-C}_4\text{H}_9$, $-\text{O}-\text{iso.-C}_4\text{H}_9$, $-\text{O}-\text{sec.-C}_4\text{H}_9$, $-\text{O}-\text{tert.-C}_4\text{H}_9$, $-\text{O}-n\text{-C}_5\text{H}_{11}$,  ,  , 
Alkoxyalkoxy:	$-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$
Aryl:	
Arylalkoxy:	 , 
Aryloxy:	
Arylalkyl:	 ,  , 
Alkenyloxy:	$-\text{O}-\text{CH}=\text{CH}_2$, $-\text{O}-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{O}-\text{CH}=\text{CH}-\text{C}_2\text{H}_5$, $-\text{O}-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2\text{CH}_3$

Alkynyloxy: $-O-C\equiv CH$, $-O-CH_2-C\equiv CH$, $-O-CH_2-C\equiv C-CH_3$
 $-O-CH_2-C\equiv C-CH_2CH_3$

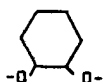
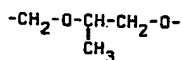
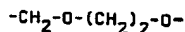
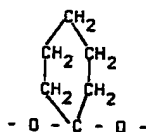
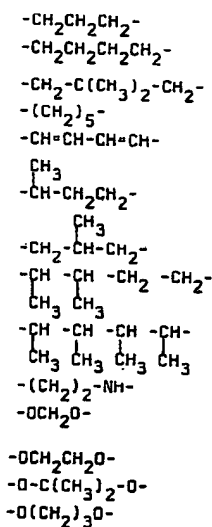
Illustrative examples of the radical $-CH(OR^{13})_2$ are:



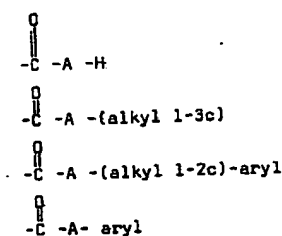
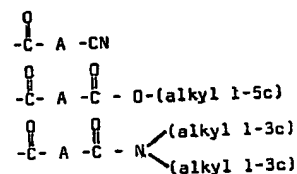
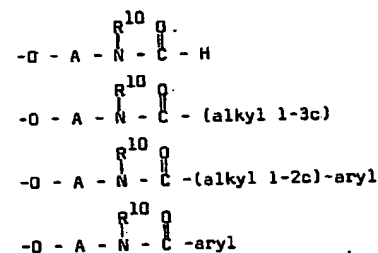
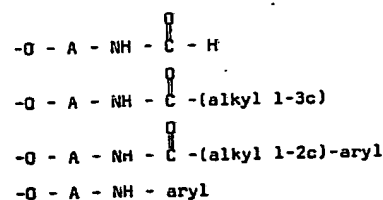
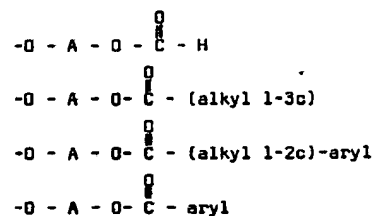
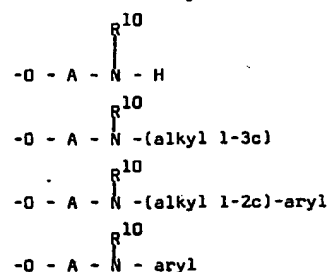
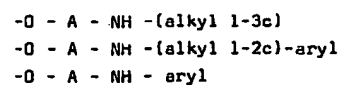
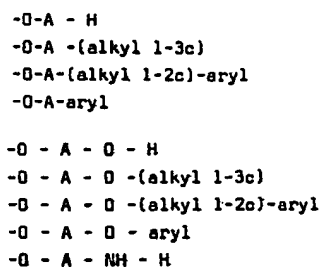
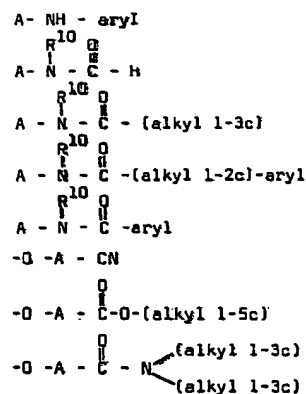
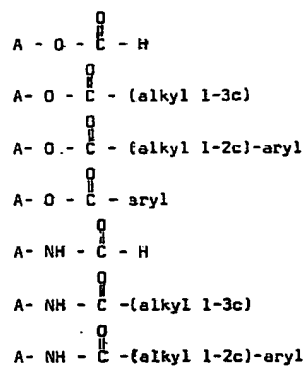
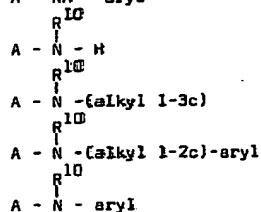
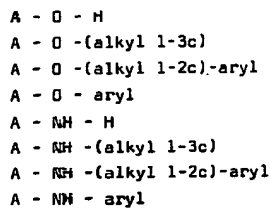
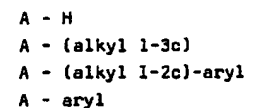
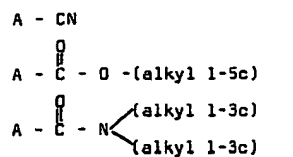
Illustrative examples of the ring structures involving R^1 , R^2 , R^3 or R^4 are



where A is



The radical $-(Z)_n-A-O$ comprises the following radicals.
 The expression (alkyl 1-3a) etc. means alkyl groups
 containing 1, 2 or 3 carbon atoms.



Further illustrative examples of the radicals in the formula I are:

alkylsulfinyl: SOCH_3 , SOC_2H_5 , $\text{SOCH}_2\text{CH}_2\text{CH}_3$, $\text{SO}-1-\text{C}_3\text{H}_7$,
 $\text{SO}-n-\text{C}_4\text{H}_9$, $\text{SO}-n-\text{C}_5\text{H}_{11}$

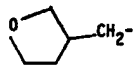
oxacycloalkyl:



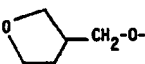
oxacycloalkoxy:



oxacycloalkyl-alkyl:



oxacycloalkyl-alkoxy:

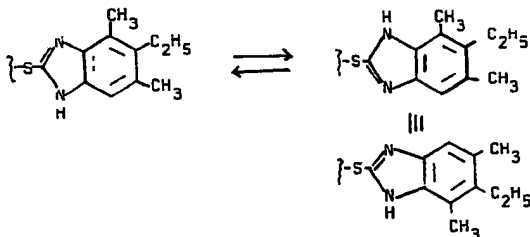


The compounds of the invention that are sulfoxides ($\text{X}=\text{SO}$) have an asymmetric centre in the sulfur atom, i.e. these compounds exist as two optical isomers (enantiomers), or if they also contain one or 5 more asymmetric carbon atoms the compounds have two or more diastereomeric forms, each existing in two enantiomeric forms. Such asymmetric carbon atoms may be the carbon atom on which R^{15} is attached (when R^{15} is other than H) or a carbon atom 10 in some of the substituents.

Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixture of the two are within the scope of the present invention. It should be understood that all the diastereomeric 15 forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

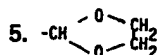
The compounds of the invention that are sulfides ($\text{X}=\text{S}$) may be asymmetric due to one or more asymmetric carbon atoms, as described above. The 20 different diastereomeric forms possible as well as the pure enantiomers and racemic mixtures are within the scope of the invention.

It should be noted that for all the compounds of the invention wherein R^5 is H the substituents R^1 and R^4 25 as well as R^2 and R^3 are considered to be equivalent. This is due to the tautomerism in the imidazole part of the benzimidazole nucleus causing an equilibrium between the two possible NH -forms. This is illustrated by the following example:



30 I Preferred groups of the radicals R^1 , R^2 , R^3 and R^4 are:

1. H
2. halogens F, Cl, Br and the groups CN, CHO, CO(aryl), COO(alkyl), CF_3 , SCH_3 , SOCH_3 and NO_2
- 35 3. the groups alkylene-D, O-alkylene-D and CO-alkylene-D wherein D is CN, COO(alkyl), COR^{10} , OR^{10} and R^{10}
4. aryl and aryloxy



40 6. $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$

7. $-\text{CH}=\text{CH}-\text{CH}=\text{C}-(\text{CH}_2)_{2-3}-$

8. saturated heterocyclic ring structures having 2 oxygen atoms.

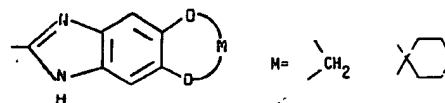
45 9. unsaturated 6-membered heterocyclic ring structures having one nitrogen atom

II Further preferred groups of the radicals R^1 , R^2 , R^3 and R^4 are:

- 50 1. H
2. halogens Cl and Br and the groups CO(phenyl), COOCH_3 , CF_3 , SCH_3 and SOCH_3
3. the groups alkyl, alkoxyalkyl, aryloxyalkyl, arylalkyl, aryl
- 55 4. the groups alkoxy, alkoxyalkoxy, aryloxyalkoxy, arylalkoxy, aryloxy
5. the group alkanoyl
6. $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$

60 7. $-\text{CH}=\text{CH}-\text{CH}=\text{C}-(\text{CH}_2)_{2-3}-$

8. saturated heterocyclic ring structures having 2 oxygen atoms in 4,5-, 5,6- or 6,7- "catechol positions", e.g. (5,6-position shown)



65 III Still further preferred groups of the radicals R^1 , R^2 , R^3 and R^4 are:

1. H
2. Br and the groups COOCH_3 and CF_3
3. the groups CH_3 , C_2H_5 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_3\text{OCH}_2\text{CH}_2-$, 70 phenyl
4. the groups CH_3O , $\text{CH}_3(\text{CH}_2)_6\text{O}$, $\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}$, (phenyl)- $\text{OCH}_2\text{CH}_2\text{CH}_2\text{O}$, (phenyl) $\text{CH}_2\text{CH}_2\text{O}$, (phenyl) O
5. the groups CH_3CO , $\text{C}_2\text{H}_5\text{CO}$
- 75 6. $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$
7. $-\text{OCH}_2\text{O}-$, $-\text{O}-$ in the 5,6- "catechol position"

IV Particularly preferred groups of the radicals R^1 , R^2 , R^3 and R^4 are:

- H, COOCH_3 , CF_3 , CH_3 , C_2H_5 , $\text{CH}(\text{CH}_3)_2$, CH_3O , 80 $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{OCH}_2\text{O}-$
- V In a preferred embodiment, at least three of the radicals R^1 , R^2 , R^3 and R^4 are other than hydrogen, or

th y form at l ast one ring.

VI In another preferred embodiment the radicals R^1 and R^2 form a ring structure

VII In another preferred embodiment the radicals R^2 and R^3 form a ring structure.

VIII In a preferred embodiment at least three of the radicals R^1 , R^2 , R^3 and R^4 are other than hydrogen.

IX In a preferred embodiment the radicals R^1 , R^2 , R^3 and R^4 are selected from H, halogen, CF_3 , alkyl and alkoxy groups.

X In a preferred embodiment the radicals R^1 , R^2 , R^3 and R^4 are selected from H, alkyl and alkoxy groups.

XI In a preferred embodiment the radicals R^1 , R^2 , R^3 and R^4 are selected from H and alkyl groups.

XII The preferred groups of X is S.

XIII The preferred group of X is SO.

XIV The preferred group of R^{15} is H.

XV Preferred groups of the radical R^5 are H, arylcarbonyl, alkoxy carbonyl, arylalkoxy carbonyl, dialkylaminocarbonyl and arylaminocarbonyl.

XVI Further preferred groups of the radical R^5 are H, phenylcarbonyl, methoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, dimethylaminocarbonyl and phenylaminocarbonyl.

XVII Particularly preferred of the radical R^5 is H.

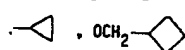
XVIII Preferred groups of the radicals R^6 and R^8 are:

1. H, CH_3 , C_2H_5 , C_3H_7 and $CH(CH_3)_2$
2. ring structures connecting position 4 in the pyridine ring.

XIX Particularly preferred groups of the radicals R^6 and R^8 are H, CH_3 , C_2H_5 and ring structures also connecting position 4 in the pyridine ring

XX Preferred groups of the radical R^7 are:

1. H, CH_3 , C_2H_5
2. OCH_3 , OC_2H_5 , $OCH_2CH_2CH_3$, $O(CH_2)_3CH_3$, OCH_2



3. $OCH_2CH=CH_2$, $OCH_2C\equiv CH$

4. $OCH_2CH_2OCH_3$, OCH_2

5. $OCH_2CH_2N(CH_3)_2$

6. $-CH=CH-CH=CH-$ bound to positions 3 and 4,

40 $-CH=CH-CH=CH-$ bound to positions 4 and 5,

$-CH_2CH_2CH_2-$ bound to positions 3 and 4,

$-CH_2CH_2CH_2-$ bound to positions 4 and 5,

$-CH_2CH_2CH_2CH_2-$ bound to positions 3 and 4,

$-CH_2CH_2CH_2CH_2-$ bound to positions 4 and 5,

45 $-OCH_2CH_2-$ bound to positions 3 and 4,

$-OCH_2CH_2-$ bound to positions 4 and 5,

$-OCH_2CH_2CH_2-$ bound to positions 3 and 4,

$-OCH_2CH_2CH_2-$ bound to positions 4 and 5,

XXI Further preferred groups of the radical R^7 are:

50 1. CH_3

2. OCH_3 , OC_2H_5 , $OCH_2CH_2CH(CH_3)_2$

3. $OCH_2CH=CH_2$

4. $OCH_2CH_2OCH_3$, OCH_2

5. $-CH_2CH_2CH_2-$ bound to positions 3 and 4,

55 $-CH_2CH_2CH_2-$ bound to positions 4 and 5,

$-CH_2CH_2CH_2CH_2-$ bound to positions 3 and 4,

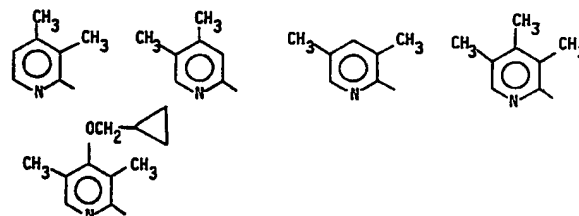
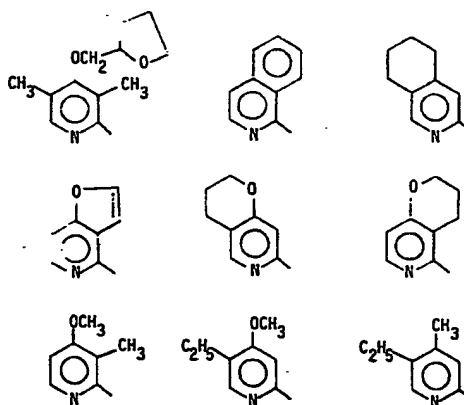
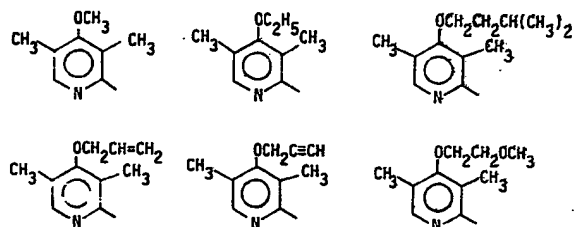
$-CH_2CH_2CH_2CH_2-$ bound to positions 4 and 5,

$-OCH_2CH_2-$ bound to positions 3 and 4, $-OCH_2CH_2-$ bound to positions 4 and 5, $-OCH_2CH_2CH_2-$ bound to positions 3 and 4, $-OCH_2CH_2CH_2-$ bound to positions 4 and 5.

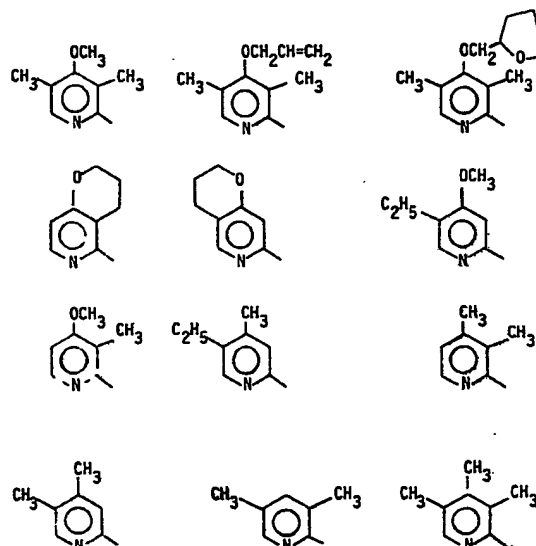
XXII Particularly preferred groups of the radical R^7 are CH_3 , OCH_3 , $OCH_2CH_2CH(CH_3)_2$, $-OCH_2$

$-OCH_2CH_2CH_2-$ bound to positions 3 and 4 or to positions 4 and 5.

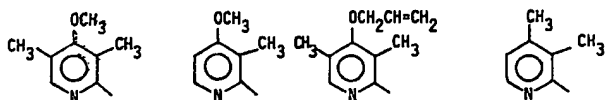
XXIII Preferred pyridyl substitution patterns are:



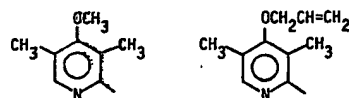
XXIV Further preferred pyridyl substitution patterns are:



XXV Still further preferred pyridyl substitution patterns are:



XXVI Particularly preferred pyridyl substitution patterns are:



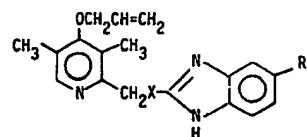
5 XXVII In a preferred embodiment two of the radicals R^6 , R^7 and R^8 form one ring structure and the third radical of R^6 , R^7 and R^8 is H.

XXVIII In a preferred embodiment R^{15} and R^5 are H, at least three times of the radicals R^1 , R^2 , R^3 and R^4 are other than H, R^6 and R^8 are H or CH_3 and R^7 is CH_3 , OCH_3 or $OCH_2CH=CH_2$.

OCH_3 or $OCH_2CH=CH_2$.

XXIX In a preferred embodiment R^{15} and R^5 are H, the radicals R^1 , R^2 , R^3 and R^4 form at least one ring structure, R^6 and R^8 are H or CH_3 and R^7 is CH_3 , OCH_3 or $OCH_2CH=CH_2$.

XXX Preferred compounds are those of the formula



wherein R^2 is alkyl or alkoxy, preferably CH_3 , C_2H_5 , $CH(CH_3)_2$ and OCH_3 , and X is S or SO.

Further illustrative examples of the radicals in the formula I are given in the examples and lists of specific compounds given elsewhere in this specification.

Illustrative examples of compounds included in the scope of the invention are given in the following

25 Table 1.

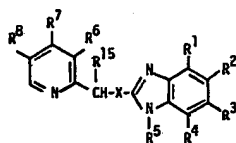


Table 1

Illustrative examples of compounds included in the scope of the invention.

X	R^{15}	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	CH_3	CH_3	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	CH_3	H	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
SO	H	CH_3	CH_3	H	CH_3	H	CH_3	$OCH_2CH=CH_2$	CH_3
S	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3
SO	H	CH_3	CH_3	H	CH_3	H	CH_3	OCH_3	CH_3
S	H	CH_3	CH_3	H	H	H	CH_3	$OCH_2CH=CH_2$	CH_3








cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	CH ₃	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	H	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	CH ₃	H	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	CH ₃	H	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	CH ₃	H	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	CH ₃	H	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	H	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ C≡CH	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ C≡CH	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	O(CH ₂) ₃ CH=CH ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	O(CH ₂) ₃ CH ₃	CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	OCH(CH ₃) ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH(CH ₃) ₂	CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	OC(CH ₃) ₃	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OC(CH ₃) ₃	CH ₃



cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃		CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	O(CH ₂) ₂ N(CH ₃) ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	O(CH ₂) ₂ N ⁺ H(CH ₃) ₂ Cl ⁻	CH ₃
S	H	H	OCH ₃	H	H	H	CH ₃	O(CH ₂) ₂ N(CH ₃) ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃
S	H	H	OCH ₃	H	H	H	H	OCH ₃	C ₂ H ₅
SO	H	H	OCH ₃	H	H	H	H	O(CH ₂) ₃ CH ₃	C ₂ H ₅
SO	H	H	OCH ₃	H	H	H	H	O(CH ₂) ₃ CH ₃	C ₂ H ₅
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH ₂ CH(CH ₃) ₂	CH ₃
SO	H	CH ₃	OCH ₃	CH ₃	H	H	H	C ₂ H ₅	CH ₃
SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH ₂ - 	CH ₃
SO	H	CH ₃	OCH ₃	CH ₃	H	H	H	CH(CH ₃) ₂	CH ₃

cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S	H	H	OCH ₃	H	H	H	H	-(CH ₂) ₄ -	
SO	H	H	OCH ₃	H	H	H	H	-(CH ₂) ₄ -	
S	H	H	OCH ₃	H	H	H	-(CH ₂) ₄ -		H
SO	H	H	OCH ₃	H	H	H	-(CH ₂) ₄ -		H
S	H	H	OCH ₃	H	H	H	H	-O-(CH ₂) ₃ -	
SO	H	H	OCH ₃	H	H	H	H	-O-(CH ₂) ₃ -	
S	H	H	OCH ₃	H	H	H	-(CH ₂) ₂ -O-		H
SO	H	H	OCH ₃	H	H	H	-(CH ₂) ₂ -O-		H
S	H	H	OCH ₃	H	H	H	H	-CH=CH-CH=CH-	
SO	H	H	OCH ₃	H	H	H	H	-CH=CH-CH=CH-	
S	H	H	OCH ₃	H	H	H	-(CH=CH-CH=CH-		H
SO	H	H	OCH ₃	H	H	H	-(CH=CH-CH=CH-		H
S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH(OCH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃











cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	H	CH(OCH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CHO	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CHO	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH=CH-COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH=CH-COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CON(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CON(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH=CH-CH	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH=CH-CH	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CH	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CH	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CH ₂ OH	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CH ₂ OH	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CH ₂ OCOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CH ₂ OCOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃










cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S	H	H	CH ₂ CH ₂ CH ₂ NHCOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ CH ₂ NHCOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH=CH-COCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH=CH-COCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH=CH- 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH=CH- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	H	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	CH ₃	H	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	O- 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃






cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S	H	H	OCH ₂ CH	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ OH	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH ₂ OH	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ OCOCH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH ₂ OCOCH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ NH ₂	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH ₂ NH ₂	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ NHCOC(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CH ₂ NHCOC(CH ₃) ₂	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CO- 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₂ CO- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CO- 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CO- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CO(CH ₂) ₃ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	CO(CH ₂) ₃ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	- 	H	H	H	CH ₃	OCH ₃	CH ₃

cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S0	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	COOCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	COOCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	COOCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	COOCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ OH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	CH ₂ OH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ OCO- 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	CH ₂ OCO- 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	COOCH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	COOCH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	C(CH ₃) ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	C(CH ₃) ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃



cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S0	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	CH ₃	H
S0	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	CH ₃	H
S	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	H	CH ₃	CH ₃
S0	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	H	CH ₃	CH ₃
S	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	H	CH ₃
S0	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	H	CH ₃
S	H	CH ₃	COC ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	CH ₃	COC ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	CH ₃	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	CH ₃	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	CH ₃
S0	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	CH ₃
S	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃

cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	H
SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	H
S	H	CH ₃	CH(CH ₃) ₂	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
SO	H	CH ₃	CH(CH ₃) ₂	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	CH(CH ₃) ₂	CH ₃	H	H	CH ₃	CH ₃	CH ₃
SO	H	CH ₃	CH(CH ₃) ₂	CH ₃	H	H	CH ₃	CH ₃	CH ₃
S	H	CH ₃	COCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
SO	H	CH ₃	COCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	Br	OCH ₃	H	H	CH ₃	OCH ₃	CH ₃
SO	H	OCH ₃	Br	OCH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	Br	OCH ₃	H	H	CH ₃	CH ₃	H
SO	H	OCH ₃	Br	OCH ₃	H	H	CH ₃	CH ₃	H
S	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃
SO	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃
S	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OC ₂ H ₅	CH ₃
SO	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OC ₂ H ₅	CH ₃
S	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃





cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	OCH ₃	H	CH ₃	H	CH ₃	OCH ₃	CH ₃
SO	H	CH ₃	OCH ₃	H	CH ₃	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	OCH ₃	H	OCH ₃	H	CH ₃	OCH ₃	CH ₃
SO	H	Cl	OCH ₃	H	OCH ₃	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₃	CH ₃
SO	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	Cl	Cl	Cl	Cl	H	CH ₃	OCH ₃	CH ₃
SO	H	Cl	Cl	Cl	Cl	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	Cl	Cl	Cl	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	Cl	Cl	Cl	Cl	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	OCH ₃	Br	H	OCH ₃	H	CH ₃	OCH ₃	CH ₃
SO	H	OCH ₃	Br	H	OCH ₃	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	Cl	Cl	OC ₂ H ₅	H	CH ₃	OCH ₃	CH ₃
SO	H	OCH ₃	Cl	Cl	OC ₂ H ₅	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	Cl	Cl	OC ₂ H ₅	H	CH ₃	CH ₃	H



cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	OCH ₃	Cl	Cl	OC ₂ H ₅	H	CH ₃	CH ₃	H
S	H	COCH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃
SO	H	COCH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃
S	H	F	Cl	H	Cl	H	CH ₃	OCH ₃	CH ₃
SO	H	F	Cl	H	Cl	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	CH ₂ COOCH ₃	Cl	H	H	CH ₃	OCH ₃	CH ₃
SO	H	Cl	CH ₂ COOCH ₃	Cl	H	H	CH ₃	OCH ₃	CH ₃
S	H	Cl	CH ₂ CH	Cl	H	H	CH ₃	OCH ₃	CH ₃
SO	H	Cl	CH ₂ CH	Cl	H	H	CH ₃	OCH ₃	CH ₃
SO	H	-CH=CH-CH=CH-		-CH=CH-CH=CH-		H	CH ₃	OCH ₃	CH ₃
S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	H	CH ₃	OCH ₃	CH ₃







cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	H	-OCH ₂ O-		H	H	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	H	CH ₃	CH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	H	CH ₃	CH ₃	CH ₃
S	H	H			H	H	CH ₃	OCH ₃	CH ₃
SO	H	H			H	H	CH ₃	OCH ₃	CH ₃
S	H	-CH=CH-CH=N-		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	-CH=CH-CH=N-		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	-CH=CH-CH=CH-		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	-CH=CH-CH=CH-		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	-CH=CH-CH=CH-		H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	-CH=CH-CH=CH-		H	H	CH ₃	OCH ₃	CH ₃
S	H	-CH ₂ CH ₂ CH ₂ CH ₂ -		H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	-CH ₂ CH ₂ CH ₂ CH ₂ -		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	-CH ₂ CH ₂ CH ₂ -		Cl	H	CH ₃	OCH ₃	CH ₃
SO	H	OCH ₃	-CH ₂ CH ₂ CH ₂ -		Cl	H	CH ₃	OCH ₃	CH ₃
S	H	OCH ₃	-CH ₂ CH ₂ CH ₂ -		Cl	H	CH ₃	OC ₂ H ₅	CH ₃





cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	OCH ₃	-CH ₂ CH ₂ CH ₂ -		Cl	H	CH ₃	OC ₂ H ₅	CH ₃
S	H		-CH=CH-CH=C-CH ₂ CH ₂ -		H	H	CH ₃	OCH ₃	CH ₃
SO	H		-CH=CH-CH=C-CH ₂ CH ₂ -		H	H	CH ₃	OCH ₃	CH ₃
S	H	H			H	H	CH ₃	OCH ₃	CH ₃
SO	H	H			H	H	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CO ₂ C ₂ H ₅	CH ₃	OCH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	CO ₂ C ₂ H ₅	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CO ₂ C(CH ₃) ₃	CH ₃	OCH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	CO ₂ C(CH ₃) ₃	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CO ₂ CH ₂ - 	CH ₃	OCH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	CO ₂ CH ₂ - 	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CO- 	CH ₃	OCH ₃	CH ₃
SO	H	H	-OCH ₂ O-		H	CO- 	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	CONH ₂	CH ₃	OCH ₃	CH ₃








cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	H		-OCH ₂ O-	H	CONH ₂	CH ₃	OCH ₃	CH ₃
S	H	H		-OCH ₂ O-	H	CONHC ₂ H ₅	CH ₃	OCH ₃	CH ₃
SO	H	H		-OCH ₂ O-	H	CONHC ₂ H ₅	CH ₃	OCH ₃	CH ₃
S	H	H		-OCH ₂ O-	H	CONHCH ₂ - 	CH ₃	OCH ₃	CH ₃
SO	H	H		-OCH ₂ O-	H	CONHCH ₂ - 	CH ₃	OCH ₃	CH ₃
S	H	H		-OCH ₂ O-	H	CONH- 	CH ₃	OCH ₃	CH ₃
SO	H	H		-OCH ₂ O-	H	CONH- 	CH ₃	OCH ₃	CH ₃
S	H	H		-OCH ₂ O-	H	CON(CH ₃) ₂	CH ₃	OCH ₃	CH ₃
SO	H	H		-OCH ₂ O-	H	CON(CH ₃) ₂	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃
SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃
S	H	H	OCH ₃	H	H	H	-CH-CH-O-		H
SO	H	H	OCH ₃	H	H	H	-CH-CH-O-		H
S	H	H	OCH ₃	H	H	H		-O-CH-CH-	
SO	H	H	OCH ₃	H	H	H		-O-CH-CH-	
S	H	H	OCH ₃	H	H	H	-CH=CH-NH-		H
SO	H	H	OCH ₃	H	H	H	-CH=CH-NH-		H
S	H	H	OCH ₃	H	H	H		-NH-CH-CH-	

cont.

cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S0	H	H	OCH ₃	H	H	H	H		-NH-CH=CH-
S	H	H	OCH ₃	H	H	H		-CH=CH-N(CH ₃)-	H
S0	H	H	OCH ₃	H	H	H		-CH=CH-N(CH ₃)-	H
S	H	H	OCH ₃	H	H	H	H		-N(CH ₃)-CH=CH-
S0	H	H	OCH ₃	H	H	H	H		-N(CH ₃)-CH=CH-
S	H	CH ₃	CH ₂ C≡CH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	CH ₃	CH ₂ C≡CH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	CH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	OCH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S0	H	H	OCH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S0	H	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	C ₂ H ₅	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	C ₂ H ₅	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	H	OCH ₃	H	H	CO- 	CH ₃	OCH ₃	CH ₃
S	H	H	H	OCH ₃	H	CO- 	CH ₃	OCH ₃	CH ₃
S0	H	H	OCH ₃	H	H	CO- 	CH ₃	OCH ₃	CH ₃

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












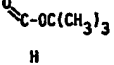
X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S0	H	H	H	OCH ₃	H	CO- 	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₃	CH ₂ OCO- 	H	CO- 	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₂ OCO- 	CH ₃	H	CO- 	CH ₃	OCH ₃	CH ₃
S	H	H	-OCH ₂ O-		H	COC ₂ H ₅	CH ₃	OCH ₃	CH ₃
S0	H	H	-OCH ₂ O-		H	COC ₂ H ₅	CH ₃	OCH ₃	CH ₃
S0	H	H	CH ₃	CH ₃	H	COOCH ₃	CH ₃	OCH ₃	CH ₃
S	H	-OC-  -CO-		H	H	H	CH ₃	OCH ₃	CH ₃
S0	H	-OC-  -CO-		H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	SOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ - 	CH ₃
S0	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ - 	CH ₃
S	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S0	H	H	CH ₃	CH ₃	H	COOC(CH ₃) ₃	CH ₃	OCH ₃	CH ₃

Table 1 cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
S	H	H	CH ₃	CH ₃	H	CON(CH ₃) ₂	CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₃	CH ₃	H	CON(CH ₃) ₂	CH ₃	OCH ₃	CH ₃
S	H	H	Br	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
SO	H	H	Br	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃
S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H
SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H
S	H	CH ₃	CH ₃	CH ₃	H	H	H	CH ₃	CH ₃
SO	H	CH ₃	CH ₃	CH ₃	H	H	H	CH ₃	CH ₃
S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	H	CH ₃
SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	H	CH ₃
S	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	CH ₃	H
SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	CH ₃	H
S	H	CH ₃	CN	CH ₃	H	H	CH ₃	OC ₂ H ₅	CH ₃
SO	H	CH ₃	CN	CH ₃	H	H	CH ₃	OC ₂ H ₅	CH ₃
SO	H	H	COOCH ₃	CH ₃	H	H	H	OCH ₃	C ₂ H ₅
S	H	H	-CH ₂ CH ₂ CH ₂ -		H	H	CH ₃	OCH ₃	CH ₃

Table 1 cont.

X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
SO	H	H	-CH ₂ CH ₂ CH ₂ -		H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₃	H	H	H	-CH ₂ CH ₂ CH ₂ O-		H
SO	H	H	OCH ₃	H	H	H	H	-OCH ₂ CH ₂ -	
S	H	H	SOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	SOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CH ₃	CH ₃	H	H	CH ₃	-OCH ₂ - 	CH ₃
SO	H	H	CH ₃	CH ₃	H	H	CH ₃	-OCH ₂ - 	CH ₃
S	H	-CH=CH-CH=CH-		-CH=CH-CH=CH-	H		CH ₃	OCH ₃	CH ₃
SO	H	H	NO ₂	H	H	H	CH ₃	OCH ₃	CH ₃
S	H	H	CF ₃	H	H	H	CH ₃	OCH ₂ - 	CH ₃
SO	H	H	CF ₃	H	H	H	CH ₃	OCH ₂ - 	CH ₃
S	H	H	CH ₂ CH ₂ COOC ₂ H ₅	H	H	H	CH ₃	OCH ₃	CH ₃
SO	H	H	OCH ₃	H	H		CH ₃	OCH ₃	CH ₃
SO	H	H	CH ₃	CH ₃	H	H	H	OCH ₃	C ₂ H ₅

The invention takes into consideration that compounds that structurally deviate from the formula I, after administration to a living organism may be transformed to a compound of formula I and in this structural form exert their effect. Such compounds structurally deviating from compounds of the formula I, are included in the scope of the invention.

Likewise, certain compounds of formula I may be metabolized into other compounds of formula I before exerting their effect. Compounds of the invention wherein X is S are thus believed to exert their antisecretory and cytoprotective activities after metabolism to compounds wherein X is SO and compounds of the invention wherein R⁵ is R¹⁴CO are believed to exert antisecretory and cytoprotective activity after metabolism to compounds wherein R⁵ is

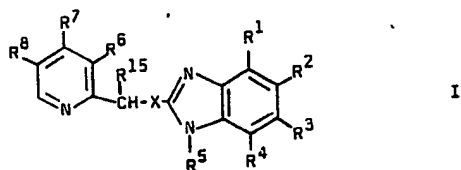
H. These considerations are also a further aspect of the invention.

Further, it is believed that all compounds of formula I wherein X is SO after administration to a living organism, exert their antisecretory and cytoprotective effects after metabolic or pure chemical transformation to another, reactive species. Accordingly, the same is true also for the compounds of formula I wherein X is S, but via initial transformation to the corresponding compounds of formula I wherein X is SO. These considerations as well as such reactive species are included within the scope of the present invention.

Preparation

Compounds of formula I above may be prepared according to the following methods:

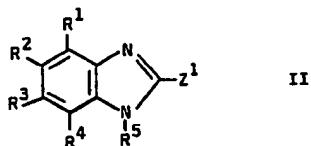
a) Oxidizing a compound of the formula I,



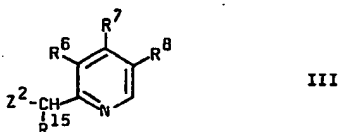
wherein X is S and R¹⁵, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ have the meanings given, to give a compound of the same formula I wherein X is SO. This oxidation may be carried out by using an oxidizing agent selected from the group consisting of nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, l-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfuric chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbially by using a suitable microorganism.

b) Reacting a compound of the formula



with a compound of the formula



in which formulas R¹⁵, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined previously and wherein one of Z¹ and Z² is SH and the other is a leaving group, gives a compound of the formula I wherein X is S.

Examples of leaving groups Z¹ and Z² in the compounds II and III are halogens, preferably chlorine, bromine or iodine, acyloxy radicals, for example residues of strong organic sulfonic acids, for instance of an arylsulfonic acid, for example tosyloxy or an alkylsulfonic acid, for example mesyloxy, alkylmercapto groups, for example methylmercapto, alkylsulfinyl groups, for example methylsulfinyl and the like.

Thus, Z¹ or Z² when designating leaving groups may be a reactive esterified hydroxy group. The esterification may be carried out with an organic acid or with an inorganic acid such as HCl, HBr or H₂SO₄.

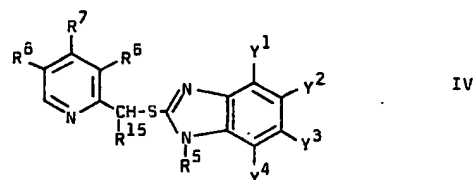
The reaction of a compound of formula II above with a compound of formula III is conveniently carried out in the presence of a suitable solvent that is inert under the reaction conditions utilized as described hereinafter. The reaction may further be carried out in the presence of a suitable base. Suitable bases include, for example, inorganic bases such as sodium

or potassium hydroxide, sodium or potassium alkoxide, sodium or potassium hydride and the like, organic bases such as tertiary amines, for example triethylamine and the like.

Suitable solvents for the above described reaction include, for example, alcohols, preferably lower alkanols such as methanol and ethanol, mixtures of such alcohols with water, ethers, such as tetrahydrofuran, halogenated hydrocarbons, such as methylene chloride. Aprotic solvents such as ethers and halogenated carbons are necessary in the case of sodium and potassium hydride.

The reaction of the compounds of formulas II and III may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture. It is preferred to carry out the reaction, however, at a temperature at or close to the boiling point of the reaction mixture for the preparation of a compound of the formula I wherein R⁵ is H.

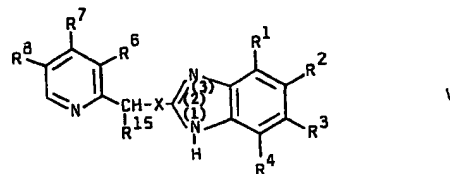
c) Esterification of a compound of the formula



wherein R¹⁵, R⁵, R⁶, R⁷ and R⁸ are as defined above and Y¹, Y², Y³ and Y⁴ represent either R¹, R², R³ and R⁴ according to the above definition, respectively, or th groups (Z)_n-A-COOH, COOH and (Z)_n-A-OH, whereby Z, n and A are as defined above, by reaction with the appropriate alcohol R⁹OH, R¹⁰OH or carboxylic acid R¹⁰COOH, respectively, to the formation of a compound of formula I containing a radical R¹, R², R³ and/or R⁴ which is either of the ester groups (Z)_n-A-COOR⁹, COOR¹⁰ or (Z)_n-A-OCOR¹⁰.

The esterification is carried out as an ordinary esterification, in the presence of an acid catalyst such as sulfuric acid, hydrochloric acid and p-toluenesulfonic acid and, if necessary, in the presence of an inert solvent such as toluene.

d) Acylation of a compound of the formula

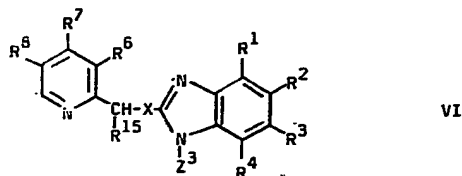


wherein R¹⁵, X, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined above, by reaction with an appropriate acylating agent (R¹⁴CO)₂O, R¹⁴COX¹, whereby X¹ is a leaving group such as Cl, N₃ and p-nitrophenoxy, R^aNCO, whereby R^a is defined by the relation R^aNH equals R¹⁴, provided that R^a is K when R¹⁴ is amino, to the formation of a compound of formula I wherein R⁵ is R¹⁴CO as defined above.

The acylation is preferably carried out in the presence of a base such as triethylamine, K₂CO₃ and NaOH and with a solvent such as tetrahydrofuran, acetonitrile and water. Normally, if the benzimidazole moiety is asymmetrically substituted, both the N(1)-

and the N(3)-acyl derivatives are obtained, and therefore, if necessary, the two components have to be separated. This may be done by recrystallizations or by extractive or chromatographic techniques.

5) Hydrolyzing a compound of the formula



wherein X, R¹⁵, R¹, R², R³, R⁴, R⁶, R⁷ and R⁸ are as defined above and Z³ is a suitable N-protecting group such as alkanoyl, carboalkoxy and trimethylsilyl, to the formation of a compound of the formula I wherein R⁵ is H.

The alkanoyl group in Z³ can have 1-6 carbon atoms and the carboalkoxy group 2-6 carbon atoms. The hydrolysis may be performed in alkaline solution or in acidic solution, the latter mainly for compounds

15 wherein X is S;

whereafter the compound of the formula I obtained if desired, when X is -S-, is converted to a physiologically acceptable salt or oxidized to form a compound of the formula I wherein X is -SO-.

20 Depending on the process conditions and the starting materials, the end products of the formula I wherein X is S is obtained either as the free base or as a salt. The end products of the formula I wherein X is -SO- are obtained as the free base. Both the free base and the salts of these end products are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. Acid addition salts of the new sulfides may in a manner known *per se* be transformed into free base using basic agents such as alkali or by ion exchange. The free bases of the sulfides obtained may also form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form

35 suitable therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfonic acid, phosphoric acid, nitric acid, and perchloric acid; aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, salicylic acid or p-aminosalicylic acid, ambonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, halogenbenzenesulfonic acid, toluenesulfonic acid, naphthylsulfonic acid or sulfanilic acids, methionin, tryptophane, lysine or arginine.

40 These or other salts of the new sulfide compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered in high purity from a new salt solution.

Racemates obtained can be separated according to

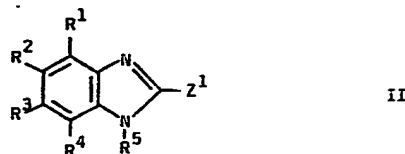
known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming diastereomeric salts which can be separated, (e.g. separation based on different solubilities of the diastereomers), acylation of the benzimidazole nitrogen (R⁵ = H) or another nitrogen or oxygen atom in a substituent by an optically active activated carboxylic acid (e.g. acid chloride), followed by chromatographic separation and deacylation.

Suitable optically active acids for salt formation are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid, and for acylation O-methylmandelic acid. Preferably the more active part of the two antipodes is isolated.

In the case of diastereomeric mixtures (racemate mixtures) these may be separated into stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystallization.

The starting materials utilized in the processes a and c-e are obtained from the process b. The starting materials used for process b are in some cases known, but in most cases unknown. These unknown starting materials may, however, be obtained according to processes known *per se*.

85 Starting materials of the formula II



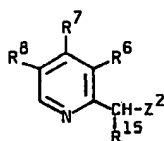
wherein Z¹ is SH may be obtained from the corresponding o-phenylenediamine by reaction with potassium ethylxanthate (Org. Synth. Vol. 30, p. 56) or thiophosgene.

90 The compounds of the formula II wherein Z¹ is alkylmercapto and alkylsulfinyl may be obtained from the above mentioned compound by simple S-alkylation with alkyl halide and by oxidation of the product from the S-alkylation, respectively.

95 The compounds of the formula II wherein Z¹ is halogen or acyloxy may be obtained from compounds of the same formula wherein Z¹ is OH by treatment with POCl₃, POBr₃ and the like or the appropriate acyl halide, respectively. The starting material wherein Z¹ is OH is obtained from the corresponding o-phenylenediamine by reaction with phosgene.

The o-phenylenediamines required may be obtained from the corresponding substituted benzenes according to processes known *per se*, e.g. by the consecutive processes: nitration, reduction, acetylation, nitration, deacetylation and reduction, or from one of the intermediary stages just mentioned. In order to obtain a o-phenylenediamine wherein R⁵ is other than H, acylation (by the group R¹⁴CO) is preferably made on the nitro-anilin stage.

Starting materials of the formula

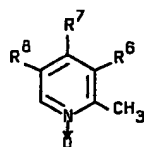


III

wherein R^{16} is H, may be obtained either from the correspondingly substituted (R^6 , R^7 and R^8) 2-methyl-substituted pyridine N-oxide via a known rearrangement to the intermediate 2-pyridinylmethanol
 5 or via a hydroxymethylation of the substituted (R^6 , R^7 and R^8) pyridine to give the same intermediate, and then treatment of the 2-pyridinylmethanol with halogenating agents such as thionyl chloride or O-acylating agents such as p-toluenesulfonyl chloride
 10 to give compounds of the formula III wherein Z^2 is halogen and sulfonyloxy groups, respectively.

These leaving groups may then be substituted for alkylmercapto groups by treatment with e.g. sodium alkylmercaptide, which may then be oxidized to an
 15 alkylsulfinyl group, or substituted for SH by treatment with e.g. NaSH.

For the preparation of intermediates of formula

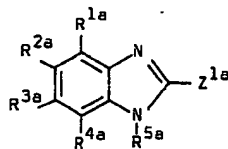


VII

wherein R^7 is alkoxy, alkenyloxy, alkynyloxy, alkoxy-alkoxy and dialkylaminoalkoxy, a compound of
 20 formula VII, wherein R^7 is NO_2 , is reacted by the corresponding sodium alkoxide. Analogously, for the preparation of an intermediate of formula VII wherein R^6 and R^7 or R^7 and R^8 form a ring structure including an oxygen atom at position 4, a compound of formula
 25 VII wherein R^7 is NO_2 and R^6 or R^8 represents hydroxyalkyl is reacted with a non-nucleophilic base.

The following intermediates A) and B) are included in the scope of the invention:

A) New compounds of the formula



VIII

30 wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are the same or different and selected from the groups

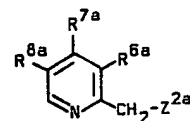
- (a) H,
- (b) alkyl containing 1-6 carbon atoms, including cycloalkyl,
- 35 (c) alkoxyalkyl containing 1-3 carbon atoms in the alkoxy part and 1-6 carbon atoms in the alkyl part,
- (d) arylalkyl containing 1-6 carbon atoms in the alkyl part,
- (e) arylalkyl containing 1-6 carbon atoms in the
- 40 alkyl part,
- (f) aryl,
- (g) alkoxy containing 1-6 carbon atoms,
- (h) alkoxyalkoxy containing 1-3 carbon atoms in the outer part and 1-6 carbon atoms in the part
- 45 nearest the aromatic ring,

(i) aryloxyalkoxy containing 1-6 carbon atoms in the alkoxy part,
 (j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and

- 50 (k) aryloxy, R^{5a} is
- (a) H,
- (b) alkoxycarbonyl containing 1-4 carbon atoms in the alkoxy part,
- 55 (c) arylalkoxycarbonyl containing 1-2 carbon atoms in the alkoxy part,
- (d) dialkylaminocarbonyl containing 1-4 carbon atoms in each alkyl group, or
- (e) arylaminocarbonyl,
- 60 and Z^{1a} is
- (a) SH,
- (b) Cl or Br

and provided that not more than one of R^{1a} , R^{2a} , R^{3a} and R^{4a} is H, are suitable intermediates for the
 65 preparation of compounds of the formula I with R^1 , R^2 , R^3 , R^4 and R^5 having the same meaning as R^{1a} , R^{2a} , R^{3a} , R^{4a} and R^{5a} , respectively, according to method b.

B) New compounds of the formula

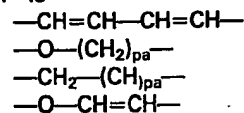


IX

wherein R^{6a} and R^{8a} are

- 70 (a) H or
- (b) alkyl containing 1-5 carbon atoms, and R^{7a} is
- (a) alkenyloxy containing 2-5 carbon atoms, or
- (b) alkynyloxy containing 2-5 carbon atoms,
- (c) oxacycloalkyl containing one oxygen atom and
- 75 3-7 carbon atoms
- (d) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
- (e) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
- 80 (f) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms,
- or

(g) R^{6a} and R^{7a} , or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridine ring form a ring
 85 wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a} is



90 wherein pa is 2, 3 or 4 and the O atom always is attached to position R^{7a} , and Z^{2a} is

- (a) SH,
- 95 (b) halogen Cl, Br, I or
- (c) OH

and provided that not more than one of R^{6a} and R^{8a} is H, are suitable intermediates for the preparation of
 compounds of the formula I with R^6 , R^7 and R^8 having
 100 the same meaning as R^{6a} , R^{7a} and R^{8a} , respectively, according to method b.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration.

The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. Since the sulfoxides of the invention are susceptible to degradation in acid to neutral media, granules and tablets containing sulfoxides are preferably coated with an enteric coating which protects the active compound from acid degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2 % to 20

% by weight of the active ingredient and the remainder consisting of sugar or sugaralcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1 % to 10 % by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Method a. Preparation of 4,6-dimethyl-5-methoxy-2-[[[3,4-dimethyl-2-pyridinyl] methyl] sulfinyl]-1H-benzimidazole.

m-Chloroperbenzoic acid, 91% (0.53 g, 0.0028 mol) dissolved in CH_2Cl_2 (25 ml) and cooled to -10°C was added under stirring to 4,6-dimethyl-5-methoxy-2-[[[3,4-dimethyl-2-pyridinyl] methyl] thio]-1H-benzimidazole (0.91 g, 0.0028 mol) dissolved in CH_2Cl_2 (50 ml) maintaining the temperature at -5°C . Stirring was continued at -5°C for 5 min and then NaOH (0.34 g, 0.0085 mol) dissolved in water (25 ml) was added under vigorous stirring. The two phases were separated and the aqueous phase was washed with CH_2Cl_2 (10 ml). More CH_2Cl_2 (50 ml) was added to the aqueous phase, the pH was adjusted to 9.5 by adding 2M HCl and after stirring the phases were separated. The organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated off giving an oil which was crystallized from CH_3CN (15 ml) yielding the desired product (0.3 g, 32%), m.p. 161°C .

Example 2. Method a. Preparation of 4,6-dimethyl-5-heptyloxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl] sulfinyl]-1H-benzimidazole.

m-Chloroperbenzoic acid, 91% (1.13 g, 0.0059 mol) dissolved in CH_2Cl_2 (25 ml) and cooled to -10°C was added under stirring to 4,6-dimethyl-5-heptyloxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl] thio]-1H-benzimidazole (2.7 g, 0.0059 mol) dissolved in CH_2Cl_2 (50 ml) maintaining the temperature at -5°C . Stirring was continued at -5°C for 10 min. The two phases were separated and then NaOH (0.26 g, 0.0066 mol) dissolved in water (50 ml) was added under vigorous stirring. The two phases were separated. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated off giving a residual oil, which according to NMR included 30% of

unreacted starting material. The oil was chromatographed on a silica column using $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ 5:95 as eluant and then the product was recrystallized from CH_3CN giving the desired product in crystalline form (0.85 g, 32%), m.p. 116°C.

Which one of these two procedures that have been used for the preparation of the different sulfoxides have been indicated in Table 2 below. For most of the compounds synthesized according to example 2 the chromatographic separation was not performed.

Example 3. Method b. Preparation of 4,6-dimethyl-5-methoxy-2-[[[3,4-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

To 4,6-dimethyl-5-methoxy-2-mercapto-1H-benzimidazole (1.04 g, 0.0050 mol) in methanol (50 ml) were added (in the following order) NaOH (0.2 g, 0.0050 mol) dissolved in water (2 ml) and 3,4-dimethyl-2-chloromethylpyridine hydrochloride (0.96 g, 0.0050 mol). The mixture was heated until reflux. NaOH (0.2 g, 0.0050 mol) dissolved in water (2 ml) was added dropwise and then the reflux was continued for 3 hours. The mixture was poured on ice-water (200 ml). Filtration and recrystallization from CH_3CN gave the desired product (1.1 g, 67%).

NMR data for the final product is given below.

Example 4 and 5. Method d. Preparation of N¹-benzoyl-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole and N¹-benzoyl-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.0 g, 0.009 mol) was dissolved in CH_3CN (30 ml) and triethylamine (1.9 ml) was added. Benzoyl chloride (1.4 g, 0.010 mol) was added dropwise under stirring during 15 min. Then the mixture was stirred at 55°C for 45 min. The solvent was evaporated off and ether was added to the residue under ice-cooling. The crystalline residue, thus obtained was stirred with water, filtered off and dried giving a white crystalline product mixture (1.9 g, 48%) of the desired two products in a 75:25 molar ratio (according to HPLC-analysis and NMR). NMR data for the final products is given below.

Example 6. Method d. Preparation of N-methoxycarbonyl-5,6-methylenedioxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

Chloro methylformate (0.24 g, 0.0026 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of 5,6-methylenedioxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (0.80 g, 0.0022 mol) and triethylamine in CH_2Cl_2 (10 ml). The mixture was then stirred at room temperature for 19 h. The CH_2Cl_2 -solution was washed with water, dried (MgSO_4) and the solvent was evaporated giving the desired product as an oil (0.06 g, 6%). NMR data for the final product is given below.

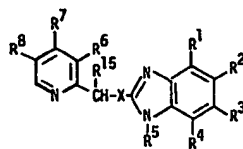
Example 7. Method d. Preparation of N¹-(N'-phenylcarbamoyl)-5,6-methylenedioxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

Phenylisocyanate (0.20 g, 0.00167 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring to a solution of 5,6-methylenedioxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (0.50 g, 0.00139 mol) and triethylamine (0.28 g, 0.00278 mol) in CH_2Cl_2 (15 ml). The mixture was then stirred at room temperature for 50 hours. The CH_2Cl_2 -solution was washed with water, dried (MgSO_4) and the solvent was evaporated giving the desired product as an oil (0.03 g, 5%). NMR data for the final products is given below.

Example 8. Method e. Preparation of 4,6-dimethyl-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. N¹-Propionyl-4,6-dimethyl-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (1.0 g, 0.0023 mol) was heated in 1M NaOH (15 ml) for 1 h under stirring and N_2 -atmosphere, pH was adjusted to 9.5 by addition of 2M HCl. Extraction with CH_2Cl_2 , separation of the phases, drying the organic phase, evaporation of the solvent and recrystallization from CH_3CN gave the desired product (0.30 g, 35%), m.p. 137°C.

The following Table 2 gives data for further examples of compounds of the invention.

Table 2. Summary of working examples.






Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
9	S	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	82	164-165
10	SO	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 2)	73	146-148
11	S	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	79	207
12	SO	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	32	193
13	S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	97	165
14	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 2)	59	147
15	S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	79	159
16	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	83	188
17	S	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	77	NMR





cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
18	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	58	129
19	S	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	79	163
20	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	52	191
21	S	H	CH ₃	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	37	109
22	SO	H	CH ₃	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	58	149
23	S	H	H	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	99	181
24	SO	H	H	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	71	157
25	S	H	CH ₃	H	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	62	NMR
26	SO	H	CH ₃	H	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	10	155
27	S	H	CH ₃	H	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	90	NMR
28	SO	H	CH ₃	H	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	69	142
29	S	H	H	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	74	NMR
30	SO	H	H	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	55	134
31	S	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	51	105-107
32	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	62	111
33	S	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ C≡CH	CH ₃	b (Ex 3)	66	154

cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
34	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ C≡CH	CH ₃	a (Ex 1)	71	145
35	SO	H	H	OCH ₃	H	H	H	H	OCH ₃	C ₂ H ₅	a (Ex 1)	31	147
36	S	H	H	OCH ₃	H	H	H	H		-(CH ₂) ₄ -	b (Ex 3)	61	NMR
37	SO	H	H	OCH ₃	H	H	H	H		-(CH ₂) ₄ -	a (Ex 2)	34	NMR
38	S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	22	148
40	S	H	CH ₃	H	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	76	134-136
41	SO	H	CH ₃	H	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	35	111
42	S	H	H	OCH ₂ CN	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	29	66
43	SO	H	H	OCH ₂ CN	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	39	94
44	S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	75	NMR
45	SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	60	155



cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
47	SO	H	H	COOCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a		
48	S	H	H	COOCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	c		
49	SO	H	H	COOCH ₂ - 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a		
50	S	H	H	CH ₂ OH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	86	192
51	SO	H	H	CH ₂ OH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	10	169
52	S	H	H	CH ₂ OCO- 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	c		
53	SO	H	H	CH ₂ OCO- 	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a		
54	S	H	H	COOCH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	75	168
55	SO	H	H	COOCH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	52	139
56	S	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	70	NMR
8	SO	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1) b (Ex 8)	56 35	137 137
3	S	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	CH ₃	H	b (Ex 3)	67	NMR
1	SO	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	CH ₃	H	a (Ex 1)	32	161
57	S	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	90	NMR
58	SO	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	68	144






cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
59	S	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	H	CH ₃	CH ₃	b (Ex 3)	95	NMR
60	SO	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	H	CH ₃	CH ₃	a (Ex 1)	58	131
61	S	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	90	192-4
62	SO	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	25	164-5
63	S	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	H	CH ₃	b (Ex 3)	99	184-6
64	SO	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	H	CH ₃	a (Ex 2)	91	148-50
65	S	H	CH ₃	COC ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	68	149
66	SO	H	CH ₃	COC ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	48	NMR
67	S	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	91	182
68	SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	67	175-7
69	S	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	H	b (Ex 3)	95	NMR
70	SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	H	a (Ex 2)	73	142-3
71	S	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	82	150
72	SO	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	81	180
73	S	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	82	143
74	SO	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	43	163

cont.





Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
75	S	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	90	204
76	SO	H	Cl	Cl	Cl	H	H	CH ₃	OCH ₃	CH ₃	a		
77	SO	H	H	CH ₃	CH ₃	H	H	H	OCH ₃	C ₂ H ₅	a (Ex 1)	43	156
78	S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	90	NMR
79	SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	61	NMR
80	S	H	H	-OCH ₂ O-		H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	91	168
81	SO	H	H	-OCH ₂ O-		H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	67	165
82	S	H		-CH=CH-CH=CH-	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	73	NMR
83	SO	H		-CH=CH-CH=CH-	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	60	184
84	S	H	H	-CH=CH-CH=CH-	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	78	191
85	SO	H	H	-CH=CH-CH=CH-	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	34	175
86	S	H		-CH ₂ CH ₂ CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	58	NMR
87	SO	H		-CH ₂ CH ₂ CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	27	175
88	S	H	H	-OCH ₂ O-		H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	d		

cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
6	SO	H	H	-OCH ₂ O-		H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	d (Ex 6)	6	NMR
7	SO	H	H	-OCH ₂ O-		H	CONH- 	CH ₃	OCH ₃	CH ₃	d (Ex 7)	5	NMR
90	S	H	H	OCH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	25	NMR
91	SO	H	H	OCH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	78	61
92	S	H	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	64	NMR
2	SO	H	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	32	116
93	S	H	H	C ₂ H ₅	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	45	NMR
94	SO	H	H	C ₂ H ₅	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 1)	49	124-6
95	S	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃	b (Ex 3)	95	NMR
96	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃	a (Ex 1)	33	111
97	S	H		-CH=CH-CH=C-CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	96	190
98	SO	H		-CH=CH-CH=C-CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	93	109
4	S	H	H	OCH ₃	H	H	CO- 	CH ₃	OCH ₃	CH ₃	d (Ex 4)	48	NMR
5	S	H	H	H	OCH ₃	H	CO- 	CH ₃	OCH ₃	CH ₃	d (Ex 5)		









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Table 2 cont.

Ex. X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data	
99 S	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	99	70	
101 S	H	H	C(CH ₃) ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	52	88-89	
102 SO	H	H	C(CH ₃) ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 2)	12	NMR	
103 S	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	84	NMR	
104 SO	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	38	118	
105 S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	58	216	
106 SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	32	158	
107 SO	H	H	OCH ₃	H	H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	d	d (Ex 4 and 5)	6	{ NMR
108 SO	H	H	H	OCH ₃	H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	d			
109 S	H	H	SCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	83	147-148	
110 S	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ 	CH ₃	b (Ex 3)	86	¹ H NMR	
111 SO	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ 	CH ₃	a (Ex 2)	89	¹ H NMR	






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Table 2 cont.

Ex. X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
112 S	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	40	¹ H NMR
113 SO	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 2)	28	123-4
114 S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	21	162
115 S	H	H	OCH ₃	H	H	H	-CH=CH-CH=CH-		H	b (Ex 3)	67	105
116 SO	H	H	OCH ₃	H	H	H	-CH=CH-CH=CH-		H	a (Ex 1)	66	100
117 S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	98	122
118 SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	80	118
119 S	H	H	OCH ₂ CH ₂ 	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	80	¹ H NMR
120 SO	H	H	OCH ₂ CH ₂ 	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	55	145 d
121 S	H	H	CO- 	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	82	¹ H NMR
122 SO	H	H	CO- 	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	24	¹ H NMR
123 S	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	88	158



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Table 2 cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method Ex. No.)	Yield %	M.p. (°C) other data
124	SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 2)	52	104
125	S	H	H	SOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	57	¹ H NMR
126	SO	H	H	SOCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	47	¹ H NMR
127	SO	H	H	NO ₂	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	14	¹ H NMR
128	S	H	H	Br	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	b (Ex 3)	64	171
129	SO	H	H	Br	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	a (Ex 2)	58	143
130	S	H	H	OCH ₃	H	H	H	-CH=CH-O-		H	b (Ex 3)	77	NMR
131	SO	H	H	OCH ₃	H	H	H	-CH=CH-O-		H	a (Ex 2)	19	NMR
132	SO	H	H	CH ₃	CH ₃	H		CH ₃	OCH ₃	CH ₃	d (Ex 6)	22	168
134	SO	H	H	CH ₃	CH ₃	H		CH ₃	OCH ₃	CH ₃	d (Ex 6)	21	¹ H NMR
135	S	H	H	CH ₃	CH ₃	H	H	CH ₃		CH ₃			
136	SO	H	H	CH ₃	CH ₃	H	H	CH ₃		CH ₃			
137	S	H	H		-CH ₂ CH ₂ CH ₂ -	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	74	160
138	SO	H	H		-CH ₂ CH ₂ CH ₂ -	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	40	171







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Table 2 cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
139	S	H		-CH=CH-CH=N-	H	H	H	CH ₃	OCH ₃	CH ₃	b (Ex 3)	38	NMR
140	SO	H		-CH=CH-CH=N-	H	H	H	CH ₃	OCH ₃	CH ₃	a (Ex 1)	26	60
141	S	H	H		-OCH ₂ O-	H	H	CH ₃	CH ₃	CH ₃	b (Ex 3)	83	193-95
142	SO	H	H		OCH ₂ O	H	H	CH ₃	CH ₃	CH ₃	a (Ex 2)	76	173
143	SO	H	H		CH ₃	H	H	H	OCH ₃	C ₂ H ₅	a (Ex 2)	49	154
144	S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H	b (Ex 3)	39	¹ H NMR
145	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H	a (Ex 2)	65	¹ H NMR
146	S	H	CH ₃	CH ₃	CH ₃	H	H	H	CH ₃	CH ₃	b (Ex 3)	78	143
147	SO	H	CH ₃	CH ₃	CH ₃	H	H	H	CH ₃	CH ₃	a (Ex 2)	64	180
148	S	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	H	CH ₃	b (Ex 3)	70	239-42
149	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	H	CH ₃	a (Ex 2)	14	171
150	S	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	CH ₃	H	b (Ex 3)	96	210
151	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	CH ₃	H	a (Ex 2)	66	¹ H NMR
152	S	H	CH ₃	CN	CH ₃	H	H	CH ₃	OC ₂ H ₅	CH ₃	b (Ex 3)	94	151
153	SO	H	CH ₃	CN	CH ₃	H	H	CH ₃	OC ₂ H ₅	CH ₃	1 (Ex 2)	29	150
154	S	H	H		H	H	H	H	CH ₃	C ₂ H ₅	b (Ex 3)	48	¹ H NMR

cont.

Table 2 cont.

Ex	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	Method (Ex. No.)	Yield %	M.p. (°C) other data
155	SO	H	H		7.	H	H	H	CH ₃	C ₂ H ₅	a (Ex 2)	44	105
156	S	H	H			H	H	H	CH ₃	OCH ₂ CH ₂ OCH ₃	b (Ex 3)	94	¹ H NMR
157	SO	H	H			H	H	H	CH ₃	OCH ₂ CH ₂ OCH ₃	a (Ex 2)	18	181
158	S	H	H	CF ₃		H	H	H	CH ₃		b (Ex 3)	67	100
159	SO	H	H	CF ₃		H	H	H	CH ₃		a (Ex 2)	57	125
160	S	H	H	CH ₂ CH ₂ COOC ₂ H ₅		H	H	H	CH ₃	OCH ₃	b (Ex 3)	15	¹ H NMR
161	SO	H	H	OCH ₃		H	H		CH ₃	OCH ₃	d (Ex 6)	50	155
163	S	H	H	OCH ₃		H	H	H	-CH ₂ CH ₂ O-	H			
164	S	H	H	OCH ₃		H	H	H	-CH ₂ CH ₂ CH ₂ O-	H	b (Ex 3)	71	¹ H NMR
165	SO	H	H	OCH ₃		H	H	H	H	-OCH ₂ CH ₂ -			
166	SO	H	H	OCH ₃		H	H	H	H	-OCH ₂ CH ₂ CH ₂ -			

Identifying data for compounds of the invention

NMR-data of the compounds in Table 2 (90 MHz)

Example No.	NMR-data: δ (CDCl ₃) ppm
17	2.3(s,3H), 2.35(d,6H), 2.5(s,3H), 2.55(s,3H), 4.4(s,2H), 4.25-4.4(d,2H), 5.2-5.6(m,2H), 5.9-6.4(m,1H), 6.9(s,1H), 8.35(s,1H).
25	
27	2.2(s,3H), 2.3(s,3H), 2.6(s,3H), 4.35-4.45(d,2H), 4.45(s,2H), 5.2-5.6(m,2H), 5.85-6.35(m,1H), 6.9-7.55(m,3H), 8.3(s,1H).
29	2.2(s,3H), 2.25(s,3H), 2.4(s,3H), 4.2-4.35(d,2H), 4.4(s,2H), 5.5-5.6(m,2H), 5.85-6.3(m,1H), 6.9-7.1(d,1H), 7.3-7.55(t,2H), 8.3(s,1H).
36	1.8(m,4H), 2.75(m,4H), 3.8(s,3H), 4.25(s,2H), 6.85(m,1H), 7.05(s,2H), 7.4(d,1H), 8.3(s,1H).
37	1.7(m,4H), 2.3-2.7(m,4H), 3.85(s,3H), 4.6(d,2H), 6.8(s,1H), 7.05(s,2H), 7.6(m,1H), 8.3(s,1H).
44	1.2-2.0(m,10H), 2.25(s,3H), 2.3(s,3H), 2.6(m,1H), 3.75(s,3H), 4.45(s,2H), 7.1(q,1H), 7.5(m,2H), 8.35(s,1H).
56	

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ (CDCl ₃) ppm
3	2.3(s,6H), 2.35(s,3H), 2.5(s,3H), 3.75(s,3H), 4.4(s,2H), 7.05-7.2(d,1H), 7.25(s,1H), 8.3-8.45(d,1H).
57	2.2(s,3H), 2.25(s,3H), 2.3(s,3H), 2.5(s,3H), 3.45(s,3H), 3.75(s,3H), 3.85(m,4H), 4.3(s,2H), 7.2(br.s., 1H), 8.3(s,1H).
59	2.3(s,6H), 2.4(s,3H), 2.55(s,3H), 3.5(s,3H), 3.9(m,4H), 4.3(s,2H), 7.2(s,1H), 7.3(s,1H), 8.4(s,1H), 9.3(br.s., 1H).
66	1.2(t,3H), 2.15(s,3H), 2.2(s,3H), 2.3(s,3H), 2.4(s,3H), 2.8(q,2H), 3.65(s,3H), 4.8(s,2H), 7.3(s,1H), 8.25(s,1H).
69	1.1(t,3H), 2.2(s,3H), 2.4(s,3H), 2.55(s,3H), 2.75(q,2H), 3.85(s,3H), 4.35(s,2H), 6.75(d,1H), 7.25(s,1H), 8.4(d,1H).
78	1.2(d,3H), 1.6(m,6H), 2.25(s,3H), 2.3(s,3H), 3.0(m,1H), 3.75(s,3H), 4.15(m,1H), 4.45(s,2H), 4.55(m,1H), 7.3(q,1H), 7.6(m,2H), 8.3(s,1H).
79	1.25(d,3H), 1.65(m,6H), 2.15(s,3H), 2.2(s,3H), 3.1(m,1H), 3.65(s,3H), 4.1(m,1H), 4.6(m,1H), 4.8(s,2H), 7.4(q,1H), 7.7(d,1H), 7.8(s,1H), 8.3(s,1H).
82	2.2(s,3H), 2.3(s,3H), 3.7(s,3H), 4.75(s,2H), 7.3-8.5(m,8H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ (CDCl ₃) ppm
86	1.85(m,4H), 2.2(s,3H), 2.25(s,3H), 2.7-3.1(m,4H), 3.75(s,3H), 4.35(s,2H), 6.9(d,1H), 7.3(d,1H), 8.25(s,1H).
6	2.2(s,3H), 2.35(s,3H), 3.8(s,3H), 4.15(s,3H), 4.75(s,2H), 6.1(s,2H), 7.3(s,1H), 7.5(s,1H), 8.15(s,1H).
7	2.15(s,3H), 2.2(s,3H), 3.7(s,3H), 4.7(s,2H), 6.05(s,2H), 7.0-7.6(m,7H), 8.15(s,1H), 8.3(s,1H).
90	2.25(s,3H), 2.1-2.4(m,2H), 2.3(s,3H), 3.75(s,3H), 4.2(t,4H), 4.4(s,2H), 6.75-7.2(m,5H), 7.2-7.6(m,3H), 8.35(s,1H).
92	0.7-2.05(m,13H), 2.25(s,3H), 2.3(s,3H), 2.35(s,3H), 2.5(s,3H), 3.65-3.9(m,2H), 3.75(s,3H), 4.35(s,2H), 7.2(s,1H), 8.3(s,1H).
93	1.25(t,3H), 2.25(s,3H), 2.3(s,3H), 2.8(q,2H), 4.4(d,2H), 4.45(s,2H), 5.2-5.65(m,2H), 5.85-6.3(m,1H), 7.0-7.65(m,2H), 7.5(s,1H), 8.35(s,1H).
95	0.9(s,3H), 1.0(s,3H), 1.5-1.95(m,2H), 2.15-2.45(m,1H), 2.25(s,3H), 2.3(s,3H), 3.7-4.0(t,2H), 3.85(s,3H), 4.45(s,2H), 2.8-7.0(m,1H), 7.15(d,1H), 7.45-7.55 (d,1H), 8.3(s,1H).
4+5	2.25(s,3H), 2.40(s,3H), 3.6 and 3.85(2s, total 3H), 3.80(s,3H), 4.8 and 4.85(2s, total 2H), 6.35-7.95 (m,8H), 8.35(s,1H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ (CDCl ₃) ppm
103	2.3(s,3H), 2.35(s,3H), 3.0(t,2H), 3.35(s,3H), 3.65(t,2H), 3.8(s,3H), 4.4(s,2H), 6.8-7.6(m,4H), 8.25(s,1H).
107+108	2.2(s,3H), 2.35(s,3H), 3.75(s,3H), 3.9 and 3.95 (2s, total 3H), 4.15(s,3H), 4.75(s,2H), 7.07-7.95 (m,3H), 8.15(s,1H).
102	1.32(s,9H), 2.08(s,3H), 2.15(s,3H), 4.09(d,2H), 4.74(s,2H), 5.10-5.45(m,2H), 5.73-6.25(m,1H), 7.28-7.73(m,3H), 8.27(s,1H).
139	2.22(s,3H), 2.29(s,3H), 3.75(s,3H), 4.40(s,2H), 7.38-7.58(m,1H), 7.87-8.02(m,2H), 8.29-8.47(m,1H), 8.70-9.00(m,2H).
110	1.25(d,6H), 1.6-2.15(m,4H), 2.25(s,3H), 2.3(s,3H), 3.0(m,1H), 3.7-4.05(m,4H), 4.25(m,1H), 4.5(s,2H), 7.15(q,1H), 7.5(s,1H), 7.55(d,1H), 8.3(s,1H).
111	1.3(d,6H), 1.55-2.15(m,4H), 2.2(s,3H), 2.25(s,3H), 3.05(m,1H), 3.65(d,2H), 3.9(m,2H), 4.2(m,1H), 4.8 (s,2H), 7.3(d,1H), 7.4-7.8(m,2H), 8.3(s,1H).
119	2.3(s,3H), 2.35(s,3H), 3.15(t,2H), 3.7(s,3H), 4.25(t,2H), 4.4(s,2H), 6.9(q,1H), 7.15(d,1H), 7.3-7.6(m,6H), 8.35(s,1H).
125	2.3(s,3H), 2.35(s,3H), 2.8(s,3H), 3.8(s,3H), 4.5 (s,2H), 7.5(d,1H), 7.75(d,1H), 8.05(s,1H), 8.4(s,1H).

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ (CDCl ₃) ppm
126	2.2(s,6H), 2.8(s,3H), 3.7(s,3H), 4.85(s,2H), 7.6(q,1H), 7.85(d,1H), 8.15(s,1H), 8.25(s,1H).
127	2.25(d,6H), 3.75(s,3H), 4.9(d,2H), 7.8(d,1H), 8.3(s,1H), 8.3(q,1H), 8.65(d,1H).
134	2.2(d,6H), 2.35(d,6H), 3:1(s,6H), 3.7(s,3H), 4.95(s,2H), 7.2(s,1H), 7.6(s,1H), 8.3(s,1H).
112	2.1(s,3H), 2.25(s,3H), 2.3(s,3H), 2.65-3.2(m,4H), 4.4(d,2H), 4.42(s,2H), 5.2-5.6(m,2H), 5.9-6.4(m,1H), 7.1(dd,1H), 7.4(d,1H), 7.5(d,1H), 8.35(s,1H).
121	2.25(s,3H), 2.35(s,3H), 3.8(s,3H), 4.45(s,2H), 7.45-8.0(m,7H), 8.15(s,1H), 8.4(s,1H).
122	2.2(s,6H), 3.7(s,3H), 4.8(d,2H), 7.5-8.05(m,7H), 8.2(s,1H), 8.25(s,1H).
144	2.25(s,3H), 2.35(s,6H), 2.38(s,3H), 2.55(s,3H), 4.4(s,2H), 7.15(d,1H), 7.3(s,1H), 8.4(d,1H).
145	2.15(s,3H), 2.23(s,3H), 2.27(s,3H), 2.4(s,3H), 2.47(s,3H), 4.8(s,2H), 7.1(d,1H), 7.3(s,1H), 8.37(d,1H).
151	2.2(s,3H), 2.23(s,3H), 2.35(s,3H), 2.4(s,3H), 2.47(s,3H), 4.8(d,2H), 7.0(s,1H), 7.1(d,1H), 8.37(d,1H).
130	3.85(s,3H), 4.65(s,2H), 6.8-7.8(m,7H), 8.55(d,1H)

NMR-data of the compounds in Table 2. (cont.)

Example No.	NMR-data: δ (CDCl ₃) ppm
131	3.85(s,3H), 4.95(d,2H), 6.65-7.60(m,7H), 8.45(d,1H).
160	1.15(t,3H), 2.20(s,3H), 2.27(s,3H), 2.49-2.73(m,2H), 2.89-3.13(m,2H), 3.72(s,3H), 4.09(q,2H), 4.37(s,2H), 6.98 and 7.08(dd,1H), 7.30-7.55(m,2H), 8.28(s,1H).
154	1.1-2.1(m,13H), 2.3(s,3H), 2.5-2.8(m,3H), 4.4(s,2H), 7.1-7.65(m,4H), 8.5(s,1H)
156	1.1-2.0(m,11H), 2.25(s,3H), 2.3(s,3H), 3.45(s,3H), 3.7(t,2H), 4.0(t,2H), 4.4(s,2H), 7.05-7.65(m,3H), 8.35(s,1H)
164 (270 MHz)	2.13(m,2H), 2.88(t,2H), 3.82(s,3H), 4.26(t,2H), 4.69(s,2H), 6.7-6.85(m,2H), 7.04(d,1H), 7.39(d,1H), 8.1(d,1H).

Preparation of intermediates

Example 11. Method A. Preparation of 4,5,7-trimethyl-2-mercapto-1H-benzimidazole.

2-Nitro-3,4,6-trimethylaniline (10.2 g, 0.057 mol) was dissolved in 95% ethanol (900 ml) and hydrogenated in the presence of Pd/C-catalyst until the theoretical amount of hydrogen had been consumed (1 hour). The whole mixture was transferred to another flask and potassium ethylxanthate (12.8 g, 0.080 mol) dissolved in water (12.5 ml) was added. The mixture was refluxed overnight, 2M NaOH (20 ml) was added and the volatiles were evaporated off. The residue was dissolved in methanol (300 ml) and the catalyst was filtered off. Part of the solvent (200 ml) was evaporated off. Water (100 ml) was added and the mixture was acidified with acetic acid (10 ml) dissolved in water (20 ml). The crystalline precipitate was filtered off, washed with water and dried under reduced pressure, giving the desired product (7.2 g, 66%), NMR: $\delta(\text{COCl}_3)$ 2.0(s,3H), 2.05(s,3H), 2.1(s,3H), 3.3(br.s,1H), 6.5(s,1H).

Example 12. Method B. Preparation of 4,6,7-trimethyl-5-methoxy-2-mercapto-1H-benzimidazole.

A solution of 4-methoxy-3,5,6-trimethyl-1,2-phenylenediamine (1.8 g, 0.010 mol) and triethylamine (2.1 g, 0.021 mol) in CHCl_3 (15 ml) was added dropwise to a stirred solution of thiophosgene (0.60 g, 0.0052 mol) in CHCl_3 (5 ml). The mixture was then stirred at room temperature for 1 hour. Water (15 ml) and triethylamine (0.5 g) was added and the mixture was stirred for 1 hour. The precipitate was filtered off, washed with water and dried in the air giving the desired product (0.96 g, 43%), NMR: $\delta(\text{COCl}_3)$

2.5(s,3H), 2.65(s,6H), 3.65(s,3H), 12.0(br.s,1H).

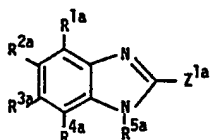
Example 13. Method C. Preparation of 4-allyloxy-3,5-dimethyl-2-pyridinyl-methanol.

4-Allyloxy-2,3,5-trimethyl-pyridine-N-oxide (4.0 g, 0.021 mol) was added dropwise under stirring to acetic anhydride (8.0 ml, 0.062 mol) preheated to 80°C, giving a final temperature of 120°C. The mixture was then heated at 80°C for 1 hour. Methanol (15.0 ml) was added and the mixture was kept at 80°C for 15 min. The volatiles were evaporated under reduced pressure. 10% HCl (20 ml) was added and the mixture was heated at 90°C for 1 hour and then cooled to room temperature. Excess 2M NaOH was added and the mixture was extracted with CH_2Cl_2 . The organic phase was separated out and dried. Volatiles were evaporated off giving the desired product as an oil (3.0 g, 75%), NMR: $\delta(\text{COCl}_3)$ 2.1(s,3H), 2.25(s,3H), 4.4(m,2H), 4.65(s,2H), 4.75(s,1H), 5.2-5.65(m,2H), 5.9-6.45(m,1H), 8.3(s,1H).

Example 14. Method D. Preparation of 4-allyloxy-3,5-dimethyl-2-pyridinyl-methyl chloride hydrochloride.

Thionyl chloride (4.0 ml) dissolved in CH_2Cl_2 (12 ml) was added dropwise to a stirred solution of 4-allyloxy-3,5-dimethyl-2-pyridinylmethanol (8.0 g, 0.041 mol) in CH_2Cl_2 (50 ml), maintaining the temperature below 6°C. Then the mixture was stirred at room temperature for 45 min (final temperature 15°C). Isopropanol (2 ml) was added and the solution was heated shortly at 35°C. The solvent was evaporated off and the crystalline residue was recrystallized from ethanol/ether giving the desired product (3.0 g, 29%), m.p. 115°C.

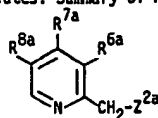
Table 3a. Intermediates. Summary of working examples.



No.	Z ^{1a}	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}	R ^{5a}	Method ^{x)} (Ex. No.)	Yield (%)	Mp (°C) other data
15	SH	CH ₃	CH ₃	CH ₃	CH ₃	H	A(Ex 11)	19	NMR
16	SH	CH ₃	CH ₃	CH ₃	H	H	A(Ex 11)	66	NMR
11	SH	CH ₃	CH ₃	H	CH ₃	H	A(Ex 11)	66	NMR
17	SH	H		H	H	H	A(Ex 11)	71	NMR
18	SH	CH ₃	OCH ₃	CH ₃	H	H	A(Ex 11)	78	NMR
19	SH	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	A(Ex 11)	85	NMR
110	SH	CH ₃	C ₂ H ₅	CH ₃	H	H	A(Ex 11)	89	NMR
111	SH	H		H	H	H	A(Ex 11)	14	167
112	SH	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	A(Ex 11)	73	NMR
12	SH	CH ₃	OCH ₃	CH ₃	CH ₃	H	B(Ex 12)	43	NMR
113	SH		-CH=CH-CH=CH-CH ₂ CH ₂ -	H	H	H	A(Ex 11)	23	NMR

^{x)} Method A: The 1,2-phenylenediamine is reacted with $\text{C}_2\text{H}_5\text{OCS}_2\text{K}$
Method B: The 1,2-phenylenediamine is reacted with CSCl_2

Table 3b. Intermediates. Summary of working examples.



No.	Z ^{2a}	R ^{6a}	R ^{7a}	R ^{8a}	Salt/Base	Method ^{xx} (Ex. No.)	Yield (%)	Mp (°C) other data
I3	OH	CH ₃	OCH ₂ CH=CH ₂	CH ₃	Base	C(Ex I3)	75	NMR
I4	Cl	CH ₃	OCH ₂ CH=CH ₂	CH ₃	HCl	D(Ex I4)	29	115°
I14	OH	CH ₃	OCH ₂ C≡CH	CH ₃	Base	C(Ex I3)	88	70°
I15	Cl	CH ₃	OCH ₂ C≡CH	CH ₃	HCl	D(Ex I4)	76	135°
I16	OH	H	-(CH ₂) ₄ -		Base	C(Ex I3)	35	NMR
I17	Cl	H	-(CH ₂) ₄ -		HCl	D(Ex I4)	72	NMR
I18	OH	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃	Base	C(Ex I3)	51	NMR
I19	Cl	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃	HCl	D(Ex I4)	95	
I20	OH	CH ₃	OCH ₂	CH ₃	Base	C(Ex I3)	30	NMR
I21	Cl	CH ₃	OCH ₂	CH ₃	HCl	D(Ex I4)	82	133
I22	OH	CH ₃	OC ₂ H ₅	CH ₃	Base	C(Ex I3)	70	B.p. 120- 26°C/0.4 mm
I23	Cl	CH ₃	OC ₂ H ₅	CH ₃	HCl	D(Ex I4)	89	157
I24	OH	-CH=CH-O-		H	Base	C(Ex I3)	18	¹ H NMR
I25	Cl	-CH=CH-O-		H	HCl	D(Ex I4)	95	195

^{xx}) Method C: Rearrangement of the pyridine N-oxide with (CH₃CO)₂O.

Method D: Chlorination with SOCl₂.

NMR—data of the compounds in Table 3a and Table 3b

Example No.	NMR-data: δ(ppm)
5 15	δ(DMSO-d ₆) 2.05(s,6H), 2.2(s,6H).
16	δ(CDCl ₃) 2.05(s,3H), 2.15(s,3H), 2.2(s,3H), 3.2(s,2H), 6.7(s,1H).
11	δ(CDCl ₃) 2.0(s,3H), 2.05(s,3H), 2.1(s,3H), 3.3(br.s,1H), 6.5(s,1H).
10 17	δ(DMSO-d ₆) 1.1-2.05(m,10H), 2.4(m,1H), 6.85-7.05(m,3H).
18	δ(DMSO-d ₆) 1.95(s,3H), 2.0(s,3H), 3.35(s,3H), 6.55(s,1H).
19	δ(CDCl ₃) 2.1(s,3H), 2.15(s,3H), 3.2(s,3H), 3.35-3.8(m,4H), 6.6(s,1H).
15 110	δ(CDCl ₃ +DMSO-d ₆) 1.05(t,3H), 2.3(s,3H), 2.35(s,3H), 2.6(q,2H), 6.85(s,1H).
112	δ(CDCl ₃) 0.5-1.7(m,13H), 2.0(s,3H), 2.1(s,3H), 3.15(s,2H), 3.35-3.6(m,2H), 6.6(s,1H).
20 12	δ(CDCl ₃) 2.5(s,3H), 2.65(s,6H), 3.65(s,3H), 12.0(br.s,1H).
113	δ(CDCl ₃) 3.35(s,2H), 3.4(s,2H), 7.15-8.05(m,4H), 12.65(br.s,1H), 13.3(br.s,1H).
25 13	δ(CDCl ₃) 2.1(s,3H), 2.25(s,3H), 4.4(m,2H), 4.65(s,2H), 4.75(s,1H), 5.2-5.65(m,2H), 5.9-6.45(m,1H), 8.3(s,1H).
116	δ(CDCl ₃) 1.5-1.9(m,4H), 2.5-2.8(m,4H), 4.7(s,2H), 7.3(s,1H), 8.2(s,1H).
30 117	δ(CDCl ₃) 1.0(s,3H), 1.05(s,3H), 1.5-2.05(m,3H), 2.15(s,3H), 2.3(s,3H), 3.75-4.0(t,2H),

4.15-4.5(br.s,1H), 4.65(s,2H), 8.3(s,1H).
120 δ(CDCl ₃) 1.7-2.2(m,4H), 2.15(s,3H), 2.25(s,3H), 3.75-4.05(m,4H), 4.15-4.4(m,1H), 4.6(s,2H), 8.25(s,1H).
124 δ(CDCl ₃) 8.55(d,1H), 7.8(d,1H), 7.5(d,1H), 7.0(d,1H), 5.1(s,2H):

Pharmaceutical preparations containing a compound of the invention as active ingredient are illustrated in the following examples.

Example 167. Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:	
4,6-Dimethyl-5-ethyl-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole-HCl	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the acid addition salt was dissolved in the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 168. Enteric-coated tablets

An enteric-coated tablet containing 20 mg of active compound was prepared from the following ingredients:

- | | | |
|----|--|--------|
| 5 | 5,6-Methylenedioxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole | 200 g |
| | Lactose | 700 g |
| | Methyl cellulose | 6 g |
| | Polyvinylpyrrolidone cross-linked | 50 g |
| 10 | Magnesium stearate | 15 g |
| | Sodium carbonate | 6 g |
| | Distilled water | q.s. |
| II | Cellulose acetate phthalate | 200 g |
| | Cetyl alcohol | 15 g |
| 15 | Isopropanol | 2000 g |
| | Methylene chloride | 2000 g |
- I 5,6 - Methylenedioxy - 2 - [[(4 - methoxy - 3,5 - dimethyl - 2 - pyridinyl)methyl]sulfinyl] - 1H - benzimidazole, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tableted cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tableting machine using 6 mm diameter punches.
- II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota, Manesty (RTM) coating equipment. A final tablet weight of 110 mg was obtained.

Example 169. Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

- | | | |
|----|--|---------|
| 40 | 4,6-Dimethyl-5-ethyl-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole | 4 g |
| | Polyethylene glycol 400 for injection | 400 g |
| | Disodium hydrogen phosphate | q.s. |
| | Sterile water to a final volume of | 1000 ml |

- 45 4,6-Dimethyl-5-ethyl-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole was dissolved in polyethylene glycol 400 and 550 ml of water was added. pH of the solution was brought to pH 7.4 by adding a water solution of disodium hydrogen phosphate and water was added to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Biological tests

I. Inhibiting effect *in vitro* on acid secretion in isolated rabbit gastric glands

Test Method**60 Gastric gland preparation**

- Isolated rabbit gastric glands were prepared as described by Berglinde et al., *Acta physi. I. scand.* 1976. 96. 150-159. This method involves vascular perfusion of the rabbit stomach via the gastric arteries, scraping and scissor mincing of the sepa-

rated gastric mucosa and collagenase (0.1%, Type I, Sigma Chemicals, St. Louis, MO. USA) digestion at 37°C for 60-90 min. The glands are then harvested and filtered through nylon cloth to remove coarse fragments. The glands are thereafter incubated at 37°C in a medium containing NaCl 132.4 mM, KCl 5.4 mM, NaH₂PO₄ 5.0 mM, NaH₂PO₄ 1.0 mM, MgSO₄ 1.2 mM, CaCl₂ 1.0 mM, glucose 10 mM, and 1 mg/ml rabbit albumine, pH 7.4.

75 Measurement of acid secretion

The acid secretion in the isolated gland preparation was recorded by measuring the uptake of ¹⁴C-labelled aminopyrine into the glands as described by Berglinde et al., *Acta physi. scand.* 1976. 97. 401-414.

- 80 Accumulation of aminopyrine in the glands indicates gastric acid secretion within the glands. The standard medium contained 10⁻⁶M ¹⁴C-aminopyrine (Amersham, Great Britain). After the incubation period, the glands were centrifuged, the supernatant was removed and the glands dried, weighed and dissolved in Soluene-350 (Packard, IU. USA). Samples of the supernatant and glands were separately counted in a scintillation counter. The accumulation of ¹⁴C-labelled aminopyrine in the glands was calculated as detailed by Berglinde et al., *Acta physi. scand.* 1976. 97. 403.

Experimental protocol

- Glands were incubated for 60 min. in the presence of 5 × 10⁻⁶M histamine and the test compound to be studied. The free base of the test compound was dissolved in methanol. The final concentration of methanol was 1% in the incubation medium, having no influence on the aminopyrine accumulation ratio. For each test compound a complete dose-response curve was generated by testing doses in duplicate in the concentration range 10⁻⁷M to 10⁻⁴M. The logarithm of the concentration (in M) of the test compounds giving 50% inhibition of the aminopyrine accumulation in the glands (IC₅₀) is listed in Table 4 below.

II. Inhibiting effect *in vivo* on gastric acid secretion in conscious dog

Test Method

- Chronic gastric fistula dogs were used. These dogs have been surgically provided with a gastric cannula in the stomach and a duodenal fistula used for direct intraduodenal administration of test compounds. Following a 4 weeks' recovery period after surgery, tests were performed once a week on each dog. Food and water were withdrawn 18 hours before each test.

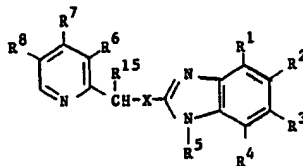
- Gastric acid secretion was induced by continuous infusion of histamine at individual doses (100-300 nmol/kg, h), resulting in submaximal secretion of gastric acid. At least 2 hours after onset of stimulation, when the gastric acid secretion had reached a steady level, the test compounds in the form of free base suspended in 0.5% Methocel (RTM) (90 HG, 15.000, Dow Chem. Corp.), were given intraduodenally at doses from 1 to 8 µmol/kg. The gastric juice was collected by free flow from the gastric cannula in consecutive 30 minutes samples for 3 hours. The samples were titrated to pH 7.0 with 0.1 M NaOH using a Radiometer automatic titrator and the acid output was calculated.

- 130 The percent inhibition of acid secretion was

calculated by comparing in each dog the acid output in the tests to the acid output in control tests when

only the vehicle was given. The peak inhibitory effect for each compound is given in Table 5 below.

Table 4 Biological effects in isolated rabbit gastric glands



No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	-log IC ₅₀
12	SO	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	6.5
16	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.5
37	SO	H	H	OCH ₃	H	H	H	H	-(CH ₂) ₄ -		5.0
43	SO	H	H	OCH ₂ CN	H	H	H	CH ₃	OCH ₃	CH ₃	4.4
51	SO	H	H	CH ₂ OH	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.1
104	SO	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	5.7
8	SO	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.5
1	SO	H	CH ₃	OCH ₃	CH ₃	H	H	CH ₃	CH ₃	H	6.7
58	SO	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	5.9
60	SO	H	CH ₃	OCH ₂ CH ₂ OCH ₃	CH ₃	H	H	H	CH ₃	CH ₃	5.4
62	SO	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.2
64	SO	H	CH ₃	COCH ₃	CH ₃	H	H	CH ₃	H	CH ₃	5.8
66	SO	H	CH ₃	COC ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.0


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No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	-log IC ₅₀
68	SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	6.5
70	SO	H	CH ₃	C ₂ H ₅	CH ₃	H	H	CH ₃	OCH ₃	H	5.9
72	SO	H	C ₂ H ₅	CN	C ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃	5.0
74	SO	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₃	CH ₃	6.2
79	SO	H	H	CH ₃ CON	H	H	H	CH ₃	OCH ₃	CH ₃	5.0
81	SO	H	H	-OCH ₂ O-		H	H	CH ₃	OCH ₃	CH ₃	6.1
83	SO	H		-CH=CH-CH=CH-	H	H	H	CH ₃	OCH ₃	CH ₃	{ 5.5 5.3
107	SO	H	H	OCH ₃	H	H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	5.8
108	SO	H	H	H	OCH ₃	H	CO ₂ CH ₃	CH ₃	OCH ₃	CH ₃	





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cont.

No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	-log IC ₅₀
10	SO	H	CH ₃	CH ₃	CH ₃	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	6.1
14	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	6.1
18	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
20	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	OCH ₃	CH ₃	6.0
22	SO	H	CH ₃	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	6.0
24	SO	H	H	CH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	6.0
26	SO	H	CH ₃	H	H	CH ₃	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
28	SO	H	CH ₃	H	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
30	SO	H	H	CH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
32	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.6
34	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ C≡CH	CH ₃	5.0
35	SO	H	H	OCH ₃	H	H	H	H	OCH ₃	C ₂ H ₅	5.6
41	SO	H	CH ₃	H	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
45	SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	6.1

cont.

cont.

No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	-log IC ₅₀
55	SO	H	H	COOCH ₃	CH ₃	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.3
87	SO	H	H	-CH ₂ CH ₂ CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	6.3
91	SO	H	H	OCH ₂ CH ₂ CH ₂ O- 	H	H	H	CH ₃	OCH ₃	CH ₃	5.8
2	SO	H	CH ₃	O(CH ₂) ₆ CH ₃	CH ₃	H	H	CH ₃	OCH ₃	CH ₃	5.9
94	SO	H	H	C ₂ H ₅	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	6.6
96	SO	H	H	OCH ₃	H	H	H	CH ₃	OCH ₂ CH ₂ CH(CH ₃) ₂	CH ₃	6.1
98	SO	H	H	-CH=CH-CH=CH-CH ₂ CH ₂ -	H	H	H	CH ₃	OCH ₃	CH ₃	5.6
102	SO	H	H	C(CH ₃) ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.9
104	SO	H	H	CH ₂ CH ₂ OCH ₃	H	H	H	CH ₃	OCH ₃	CH ₃	5.7
106	SO	H	H		H	H	H	CH ₃	OCH ₃	CH ₃	6.0
111	SO	H	H	CH(CH ₃) ₂	H	H	H	CH ₃	OCH ₂ - 	CH ₃	6.2
113	SO	H	H	CH ₂ CH ₂ COCH ₃	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	5.8
118	SO	H	H	O- 	H	H	H	CH ₃	OCH ₃	CH ₃	6.4

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



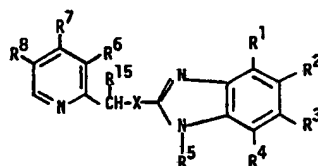
No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	-log IC ₅₀
120	SO	H	H	OCH ₂ CH ₂ - 	H	H	H	CH ₃	OCH ₃	CH ₃	6.3
124	SO	H	H	- 	H	H	H	CH ₃	OCH ₃	CH ₃	7.0
129	SO	H	H	Br	H	H	H	CH ₃	OCH ₂ CH=CH ₂	CH ₃	
142	SO	H	H		-OCH ₂ O-	H	H	CH ₃	CH ₃	CH ₃	6.0
143	SO	H	H		CH ₃	H	H	H	OCH ₃	C ₂ H ₅	6.1
145	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H	6.2
147	SO	H	CH ₃	CH ₃	CH ₃	H	H	H	CH ₃	CH ₃	6.4
149	SO	H	CH ₃	CH ₃	CH ₃	H	H	CH ₃	H	CH ₃	6.2
151	SO	H	CH ₃	CH ₃	H	CH ₃	H	CH ₃	CH ₃	H	6.3
153	SO	H	CH ₃	CN	CH ₃	H	H	CH ₃	OC ₂ H ₅	CH ₃	5.2
77	SO	H	H	CH ₃	CH ₃	H	H	H	OCH ₃	C ₂ H ₅	6.0
159	SO	H	H	CF ₃	H	H	H	CH ₃	OCH ₂ - 	CH ₃	6.3

Table 5 Biological effects in conscious dogs



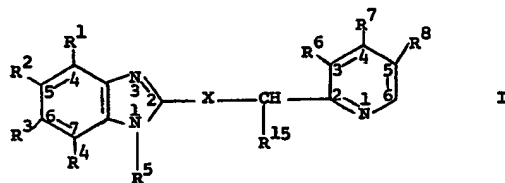
No.	X	R ¹⁵	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	(I.D.) DOSE (μmol/kg)	% INHIB	
84	S	H	H		-CH=CH-CH=CH-	H	H	CH ₃	OCH ₃	CH ₃	8	85	
109	S	H	H	SCH ₃		H	H	H	CH ₃	OCH ₃	CH ₃	8	60

Comment to the test results

It is seen in Table 4 and Table 5 that the tested compounds potently inhibited gastric acid secretion both in vitro and in vivo.

5 CLAIMS

1. A compound of the formula



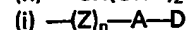
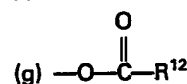
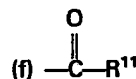
wherein

X is —S— or —S— ;
 R^{15} is H, CH₃ or C₂H₅;

10 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 , which are the same or different, are

- (a) H
- (b) halogen
- (c) —CN
- (d) —CHO

15 (e) —CF₃



20 (j) aryl

(k) aryloxy

(l) alkylthio containing 1-6 carbon atoms

(m) —NO₂

(n) alkylsulfinyl containing 1-6 carbon atoms or

25 wherein

(o) adjacent groups $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring which rings may be

30 saturated or unsaturated and may contain 0-3 hetero atoms selected from —N— and —O—, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon

atoms, alkylene radicals containing 4-5 carbon atoms

35 giving spiro compounds, or two or four of these substituents together form one or two oxo groups.

$$\begin{array}{c} \text{O} \\ || \\ (-\text{C}-), \end{array}$$
 where by if R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12} , which are the

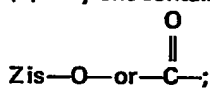
5 same or different, are

- (a) aryl,
- (b) alkoxy containing 1-4 carbon atoms,
- (c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part,
- 10 (d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part,
- (e) aryloxy,
- (f) dialkylamino containing 1-3 carbon atoms in each alkyl residue, or

15 (g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is (a) alkyl containing 1-4 carbon atoms, or

(b) alkylene containing 2-3 carbon atoms;



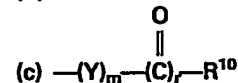
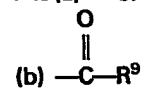
20 n is 0 or 1;

- A is (a) alkylene containing 1-6 carbon atoms
- (b) cycloalkylene containing 3-6 carbon atoms
- (c) alkenylene containing 2-6 carbon atoms
- (d) cycloalkenylene containing 3-6 carbon atoms,

25 or

(e) alkynylene containing 2-6 carbon atoms;

D is (a) $-\text{CN}$



30 wherein

- R^9 is (a) alkoxy containing 1-5 carbon atoms, or
- (b) dialkylamino containing 1-3 carbon atoms in each alkyl residue;

m is 0 or 1;

35 r is 0 or 1;

Y is (a) $-\text{O}-$

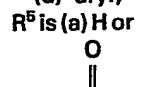
(b) $-\text{NH}-$

(c) $-\text{NR}^{10}-$;

R^{10} is (a) H

- 40 (b) alkyl containing 1-3 carbon atoms,
- (c) arylalkyl containing 1-2 carbon atoms in the alkyl part, or
- (d) aryl;

R^5 is (a) H or



45 wherein

- R^{14} is (a) alkyl containing 1-6 carbon atoms,
- (b) arylalkyl containing 1-2 carbon atoms in the alkyl part

50 (c) aryl

- (d) alkoxy containing 1-4 carbon atoms
- (e) arylalkoxy containing 1-2 carbon atoms in the alkyl part

(f) aryloxy

55 (g) amino

(h) mono- or dialkylamino containing 1-4 carbon atoms in each alkyl residue

(i) arylalkylamino containing 1-2 carbon atoms in the alkyl part

60 (j) arylamino;

R^6 and R^8 , which are the same or different, are

(a) H or

(b) alkyl containing 1-5 carbon atoms;

R^7 is (a) H

65 (b) alkyl containing 1-8 carbon atoms

(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyloxy containing 2-5 carbon atoms

70 (f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group

(g) dialkylaminoalkoxy containing 1-2 carbon

atoms in each of the alkyl residues on the amino nitrogen and 1-4 carbon atoms in the alkoxy group

(h) oxacycloalkyl containing one oxygen atom and

75 3-7 carbon atoms

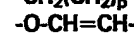
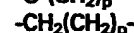
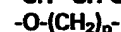
(i) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms

(j) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

80 (k) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(l) R^6 and R^7 , or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring from a ring wherein the part constituted by R^6 and R^7 , or R^7 and

85 R^8 , is



90 $-\text{NH}-\text{CH}=\text{CH}-$



wherein p is 2, 3 or 4 and the O and N atoms always are attached to position 4 in the pyridine ring; and physiologically acceptable salts of the compounds I wherein X is S;

with the provisos that

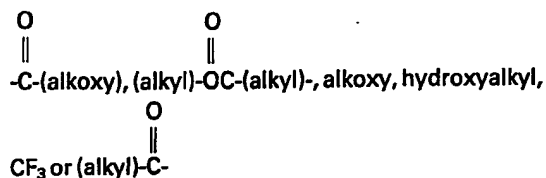
(a) not more than one of R^6, R^7 and R^8 is hydrogen,

100 (b) when X is SO, R^5 is H and R^6, R^7 and R^8 are selected only from hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which

105 are not H cannot be selected only from alkyl groups, halogen, alkoxycarbonyl, alkoxy or alkanoyl.

(c) when X is S, R^5 is H, alkanoyl or alkoxycarbonyl, and R^6, R^7 and R^8 are selected only from hydrogen, methyl, ethyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl groups, halogen, alkoxycarbonyl, alkoxy, alkanoyl, trifluoromethyl, or NO_2 .

115 (d) when X is SO, one of R^6, R^7 and R^8 is H and the other two of R^6, R^7 and R^8 are alkyl, and at the same time more than one of R^1, R^2, R^3 and R^4 are hydrogen, then those radicals R^1, R^2, R^3 and R^4 which are not H cannot be selected only from alkyl, halogen, cyano,



(e) when R^3, R^4, R^5 and R^{15} are H and simultaneously R^6 and R^8 are H or CH_3 and R^7 is OCH_3 , then R^1 is not CF_3 when R^2 is H, and R^2 is not CF_3 when R^1 is H.

2. A compound according to claim 1 wherein $X=\text{S}$.

3. A compound according to claim 1 wherein $X=\text{SO}$.

10: 4. A compound according to any one of the preceding claims wherein $R^5=\text{H}$.

5. A compound according to any one of the preceding claims wherein $R^{15}=\text{H}$.

15 6. A compound according to any one of the preceding claims wherein at least three of the radicals R^1, R^2, R^3 and R^4 are other than hydrogen, or they form at least one ring.

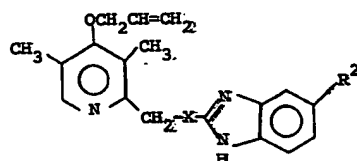
7. A compound according to any one of the preceding claims wherein R^1, R^2, R^3 and R^4 are selected from H, alkyl and alkoxy groups.

8. A compound according to any one of the preceding claims wherein R^6 and R^8 are selected from H, CH_3 , C_2H_5 , C_3H_7 , $\text{CH}(\text{CH}_3)_2$ and ring structures connecting with position 4 in the pyridine ring.

25 9. A compound according to any one of the preceding claims wherein two of the radicals R^6, R^7 and R^8 form one ring structure and the third radical of R^6, R^7 and R^8 is H or alkyl.

30 10. A compound according to any one of claims 1-8 wherein R^5 and R^{15} are H; at least three of the radicals R^1, R^2, R^3 and R^4 are other than H; R^6 and R^8 are each H or CH_3 ; and R^7 is CH_3 , OCH_3 or $\text{OCH}_2\text{CH}=\text{CH}_2$.

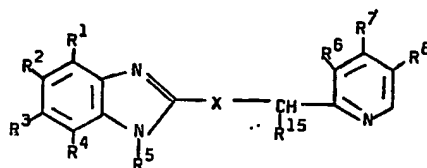
11. A compound of the formula:



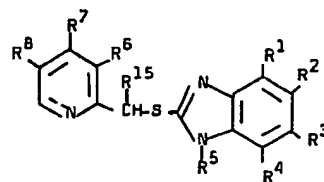
35 wherein X is S or SO

R^2 is CH_3 , C_2H_5 , $\text{CH}(\text{CH}_3)_2$ or OCH_3 .

12. A process for the preparation of a compound of the formula:



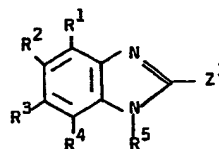
40 wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^{15} are as defined in claim 1, and X is SO by oxidizing a compound of the formula I,



I

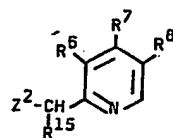
wherein $R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7$ and R^8 have the meanings given above, to give a compound of the same formula I wherein X is SO;

45 13. Process for preparation of a compound of the formula I wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^{15} are as defined in claim 1 and X is S by reacting a compound of the formula:



II

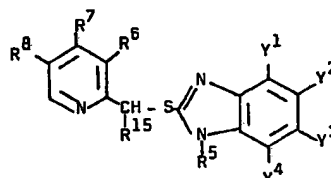
50 with a compound of the formula:



III

in which formulae $R^{15}, R^1, R^2, R^3, R^4, R^5, R^6, R^7$ and R^8 are as defined in claim 1 and wherein one of Z^1 and Z^2 is SH and the other is a leaving group, to give a compound of the formula I wherein X is S.

55 14. Process for the preparation of a compound of the formula I wherein X is S and at least one of R^1, R^2, R^3 and R^4 is an ester group $(Z)_n\text{-A-COOR}^9$, COOR^{10} or $(Z)_n\text{-A-OCOR}^{10}$ wherein Z, n, A, R^9 and R^{10} are as defined in claim 1 by esterification of a compound of the formula:

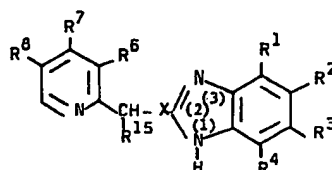


IV

wherein R^{15}, R^5, R^6, R^7 and R^8 are as defined in claim 1 and Y^1, Y^2, Y^3 and Y^4 represent either R^1, R^2, R^3 and R^4 as defined in claim 1, respectively, or the groups

65 $(Z)_n\text{-A-COOH}$, COOH and $(Z)_n\text{-A-OH}$, but at least one of Y^1, Y^2, Y^3, Y^4 is in the acid or alcohol form, by reaction with the appropriate alcohol $R^9\text{OH}$, $R^{10}\text{OH}$ or carboxylic acid $R^{10}\text{COOH}$, respectively, to form the required compound.

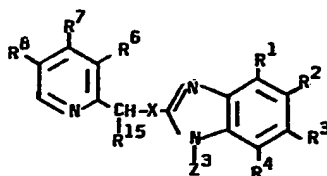
70 15. Process for preparation of a compound of the formula I wherein R^5 is $R^{14}\text{CO}$ and R^{14} is as defined in claim 1, by acylation of a compound of the formula:



V

wherein R^{15} , X , R^1 , R^2 , R^3 , R^4 , R^6 , R^7 and R^8 are as defined in claim 1, by reaction with an appropriate acylating agent ($R^{14}CO^2O$, or $R^{14}COX^1$, wherein X^1 is a leaving group.

- 5 16. Process for the preparation of a compound of the formula I wherein R^5 is H, by hydrolyzing a compound of the formula



VI

- wherein X , R^{15} , R^1 , R^2 , R^3 , R^4 , R^6 , R^7 and R^8 are as defined in claim 1 and Z^3 is a suitable N-protecting group to form the required compound.
- 10 17. A process according to any one of claims 13-16 wherein a compound in which X is S is obtained and the resulting compound is converted into a physiologically acceptable salt.
- 15 18. A process according to any one of claims 12-17 substantially as hereinbefore described with reference to any one of the Examples.
19. A pharmaceutical composition containing a compound or salt according to any of claims 1-11
- 20 together with an inert carrier or diluent.
20. A composition according to claim 19 substantially as hereinbefore described with reference to any one of Examples 167-169.
21. A compound according to any one of claims 25 1-11 or a physiologically acceptable salt thereof or a composition according to claim 19 or 20 for use in a method of treatment of the human or animal body by surgery or therapy.
22. A compound according to any one of claims 30 1-11 or a physiologically acceptable salt thereof or a composition according to claim 19 or 20 for use in the treatment of gastric disorders.
23. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use in inhibiting gastric acid secretion in the human or animal body.
24. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use as a gastrointestinal cytoprotecting agent in the human or animal body.
25. A compound as defined in any of claims 1-11, or a therapeutically acceptable salt thereof, or a composition according to claim 19 or 20 for use in the treatment of gastrointestinal inflammatory diseases in the human or animal body.
26. A compound of the formula:



VIII

- wherein R^{1a} , R^{2a} , R^{3a} and R^{4a} are the same or different and selected from the groups

- (a) H,
(b) alkyl containing 1-6 carbon atoms including cycloalkyl
(c) alkoxyalkyl containing 1-3 carbon atoms in the
55 alkoxy residue and 1-6 carbon atoms in the alkyl residue,
(d) aryloxyalkyl containing 1-6 carbon atoms in the alkyl residue,
(e) arylalkyl containing 1-6 carbon atoms in the
60 alkyl residue,
(f) aryl,
(g) alkoxy containing 1-6 carbon atoms,
(h) alkoxyalkoxy containing 1-3 carbon atoms in the outer alkoxy residue and 1-6 carbon atoms in the
65 alkoxy residue nearest the aromatic ring.
(i) aryloxyalkoxy containing 1-6 carbon atoms in the alkoxy residue,
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy residue, and
70 (k) aryloxy,
 R^{5a} is (a) H,
(b) alkoxycarbonyl containing 1-4 carbon atoms in the alkoxy residue,
(c) arylalkoxycarbonyl containing 1-2 carbon
75 atoms in the alkoxy residue,
(d) dialkylaminocarbonyl containing 1-4 carbon atoms in each alkyl residue, or
(e) arylaminocarbonyl,
and Z^{1a} is (a) SH,
80 (b) Cl or Br
provided that not more than one of R^{1a} , R^{2a} , R^{3a} and R^{4a} is H.

27. A compound of the formula:



IX

- wherein R^{6a} and R^{8a} are
- 85 (a) H or
(b) alkyl containing 1-5 carbon atoms, and
 R^{7a} is (a) alkenyloxy containing 2-5 carbon atoms, or
(b) alkynyloxy containing 2-5 carbon atoms,
90 (c) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms,
(d) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms,
(e) oxacycloalkylalkyl containing one oxygen atom
95 and 4-7 carbon atoms
(f) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(g) R^{6a} and R^{7a} , or R^{7a} and R^{8a} together with the adjacent carbon atoms in the pyridine ring form a ring
100 wherein the part constituted by R^{6a} and R^{7a} or R^{7a} and R^{8a} is
—CH=CH—CH=CH—
—O—(CH₂)_{pa}—
—CH₂—(CH₂)_{pa}—
105 —O—CH=CH—
wherein pa is 2, 3 or 4 and the O atom always is attached to position R^{7a} ,
and Z^{2a} is (a) SH,
(b) halogen Cl, Br, I or

(c) OH
provided that not more than one of R^{6a} and R^{8a} is H.

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